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FORMATION OF SINGLE-OVUM TWINS

By George L. Streeter,

Department of Embryology, Carnegie Institution of Washington

It has recently been the writer's privilege to study the Mateer ovum, a very young, well-preserved specimen containing twin embryos. The larger embryo is in the primitive-groove stage, having an embryonic plate 0.92 mm. long and 0.78 mm. wide. In its form and attachment to the chorionic membrane it is entirely normal and, judging from the best criteria we have at present, it has a development of about 17 days.[1] The smaller embryo consists of an amniotic vesicle 0.1 mm. in its largest internal diameter, and a yolk-vesicle (0.03 mm. internal diameter) slightly detached from it, the two being suspended in the loose mesenchyme in the region of the body-stalk of the co-twin. The position of these vesicles and their relation to the larger embryo are shown in Fig. 1. The chorionic membrane with its villi and trophoblast can be recognized above, while below is shown the yolk-sac of the larger embryo, cut transversely through the region of the body-stalk. Among the loose strands of parietal mesoblast intervening between these can be seen the two detached vesicles which together constitute the very much smaller twin.

The detailed structure of the amniotic vesicle of the smaller embryo is shown in Fig. 2, where its wall can be seen to be made up of an ectodermal layer clearly subdivided into amniotic ectoderm and a thicker plate below of embryonic ectoderm, which is to form the embryonic shield. The ectodermal layer is everywhere surrounded by an irregular membranous layer of mesoderm. The wall of the yolk-sac consists of a single layer of endodermal cells (see Fig. 3) and, like the amnion, is inclosed in a layer of mesodermal tissue. In general form the amniotic vesicle appears to be normal and corresponds in many respects to those seen in the ova described by Peters, Fetzer, Jung and Strahl-Beneke. It differs from those, however, in being completely detached from the yolk-sac, and in this respect is probably abnormal.

Among the first 2500 specimens in the Carnegie Embryological Collection there are 43 instances of twinning, which is about what would be expected in that number of births if we assume the frequency to vary between 1 and 2 per cent. In nine of these specimens the embryos are not over 20 mm. long—that is, less than eight weeks old—but in only two are they under 5 mm. One of these is the Mateer specimen which I am describing; the other is a pathological specimen (No. 825) which was obtained by Dr. Cecil Vest at operation for tubal pregnancy. In this case the tube contained two chorions undergoing hydatiform degeneration. Sections of these show respective internal diameters of 14 x 12 mm. and 14 x 10 mm.

[1] For a complete description of this embryo see "A human embryo (Mateer) of the presomite period." Contributions to Embryology, Vol. 9, 1919. Carnegie Inst. Wash., Pub. No. 272.

Neither chorion contains an amnion, and in only one is there any remnant of an embryo (a nodule 2.5 mm. long). In size and character the chorions correspond to those seen in normal ova about four weeks old. The specimen represents, therefore, about the same stage of development as the Watt (1915) twins, in which there were 17-19 paired somites. The Chidester specimen (mentioned by Newman, 1917, p. 68) was at first thought to be twins, one embryo having a development of one month, while the other was supposedly in the primitive-

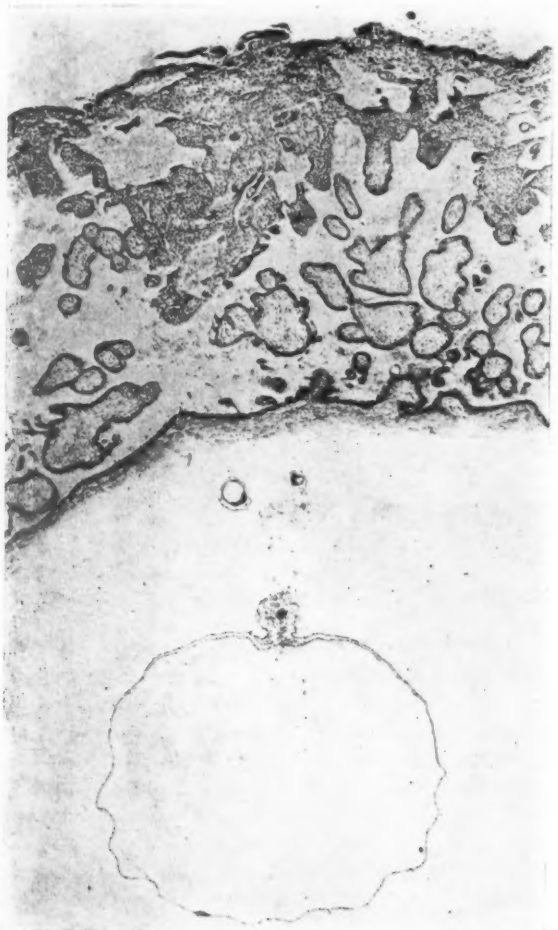

FIG. 1.—Section of the Mateer ovum showing yolk-sac and body-stalk of the primary embryo, between which and the chorionic membrane are two small ectodermic vesicles constituting the amniotic and yolk vesicles of a twin embryo. × 34.

streak stage. Subsequent study, however, has shown that the smaller structure was not really a twin. If, then, we disregard this specimen, that of Watt constitutes the youngest reported case of human twinning.

The Mateer ovum is considerably younger than the Watt specimen. Whereas the latter is in the stage of 17 somites, the primary Mateer embryo is in the presomite stage and has only just acquired a primitive groove, while the accompanying twin has attained an even lesser degree of development. The fact, therefore, that it affords the earliest picture of twin formation that has thus far been seen, lends to this specimen a particular interest. Furthermore, it possesses additional importance in that it shows this early stage of the twinning process in a single ovum. Both the Watt specimen and No. 825, mentioned above, are double-ovum twins.

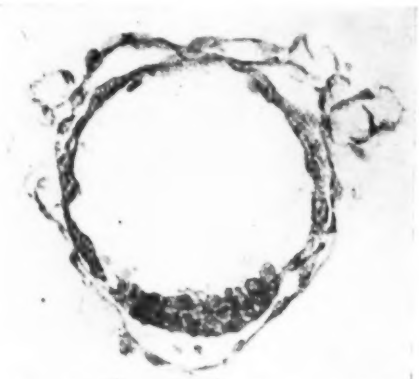

FIG. 2.—Amniotic vesicle of the twin embryo showing the thicker embryonic plate below already differentiated from the thinner amniotic ectoderm. The vesicle is surrounded by an irregular membranous layer of mesoderm. × 400.

The exact character of the mechanism by which human twins are derived from a single ovum is still unknown. There are, however, certain mammals in which polyembryony is the normal occurrence, and where it has been possible to obtain all the stages of the process. This is the case in the nine-banded armadillo which has been carefully studied by Newman (1917) and Patterson (1913). According to these authors, at a time

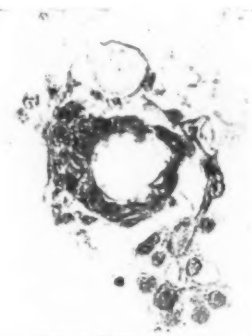

FIG. 3.—Yolk-sac of twin embryo enclosed by an irregular layer of mesoderm. × 400.

when the single amniotic vesicle has reached a considerable amount of differentiation there occurs a physiological isolation of four secondary areas in its wall which undergo independent growth and development, giving rise to four individual embryos with a common amnion. This departs from the conditions existing in human twins, since in the latter there are two separate amnions. This is also the case in sheep.

Very young sheep twins, not more than seven days old, have been described by Assheton. His specimen consists of a blastocyst 0.9 x 0.7 mm., containing two germinal areas, each apparently perfect and presumably capable of forming a perfect embryo. They were completely separated and in each of them the embryonic mass consisted of a compact cluster of ectodermal cells with a thin endodermal membrane extending a short distance from its margins—the uncompleted yolk-sac. There was a slight difference in size between the two areas and both were smaller than normal germinal areas in the same stage of development. Assheton regarded his specimen as having been produced by fission, or a mechanical splitting apart of the original germinal mass, at the time of the formation of the blastodermic vesicle, which he thinks is rendered more likely in such animals as the sheep, in which the cavity of the blastocyst is produced by an irregular cleft formation which tends to subdivide the embryonic mass. The direction of the line of fission was a matter of concern to Assheton, who thought that only sagittal fission could produce twins and double monsters. Transverse fission separating primary and secondary centers of growth of the embryo he believes to be incapable of producing embryos that would subsequently grow and develop.

Although apparently meeting the requirements in the sheep, it is not probable that this simple mechanical explanation presented by Assheton will be sufficient to explain certain features of the problem occurring in other forms. There is doubtless, as Newman argues, a large physiological element which is not to be explained on morphological grounds. In this connection reference may be made to the interesting experiments of Lewis (1910), who found that small lateral fragments of the medullary plate in the region of the hind-brain, when transplanted, tend to develop individually into a bilaterally symmetrical medulla oblongata, with a characteristic ventricle, roof, and the typical arrangement of white and gray substance. In my own experiments on the otocyst I always found that fractional parts of the otic cup, when transplanted, tend to form completely closed vesicles, although in this organ there is marked predetermination of tissue. We should, therefore, naturally expect that subdivision into two masses of such a primitive and undifferentiated tissue as the embryonic node would result in the formation of two embryos having all the potentialities of the original node.

The earliest stage of development that has been observed in the human embryo is the one described by Miller. In his specimen the embryo, or embryonic node, consists of a solid cell mass undergoing cleft formation preliminary to the opening up of the amniotic cavity. The embryo and the tissue from which the exocœlom is formed are inclosed by a trophoblastic shell of ectoderm possessing irregular syncytial loops which tend to enclose the large blood lacunæ surrounding the ovum, there being as yet no villi. This stage is shown in Fig. 5, A. Instead of a single embryo, as was the case in the Miller specimen, the embryonic node is represented as having subdivided into two masses—that is, as having given off a hypothetical twin. It is conceivable that the chances of the secondary bud reaching maturity would depend upon how large a share of the original mass is contributed to it. If the twin is as large as the primary embryo their chances of developing in an orderly manner would be equal, and this is presumably the case in most instances of identical twins. Where the secondary bud is merely a fragment of the original mass we should expect that, like the fragments of medullary plate in the Lewis experiments, there would be some degree of differentiation; but the process of development would soon be arrested, and at term the stunted bud would be found as a small epithelial cyst on the placenta near the attachment of the umbilical cord. In case the twin-bud is only partially detached from the primary node there would exist the basis for the various types of double monsters and teratomata.

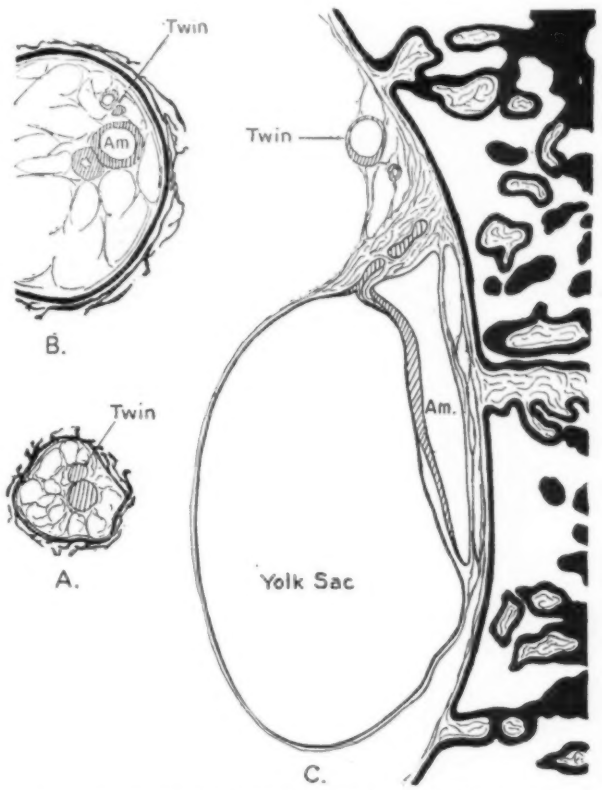

FIG. 5.—Schematic drawing, showing the probable steps in the formation of a single-ovum twin. The stages are drawn at the same scale of enlargement so that they may be directly compared. A. Stage corresponding to the Miller specimen, showing a hypothetical twin budding off from the primary embryonic node. B. Stage corresponding to the Bryce-Teacher specimen. C. The Mateer specimen. The relatively small size of the twin in this specimen, and the detachment of the yolk sac from the amniotic vesicle are indications of arrest in development.

A slightly more advanced stage is schematically shown in Fig. 5, B, which may be compared to the conditions existing in the well-known Bryce-Teacher specimen. Here, both embryonic masses have developed into ectodermal (amniotic) vesicles, and at the same time small yolk-sacs are forming near them and probably from cells derived from their wall The transition from stage B to stage C may be readily followed

the latter showing the conditions existing in the Mateer specimen. Here the size of the cavity of the yolk-sac has surpassed that of the amnion, a definite body-stalk has formed, and near it are the two vesicles constituting the twin, which, as compared with the primary embryo, is considerably retarded in

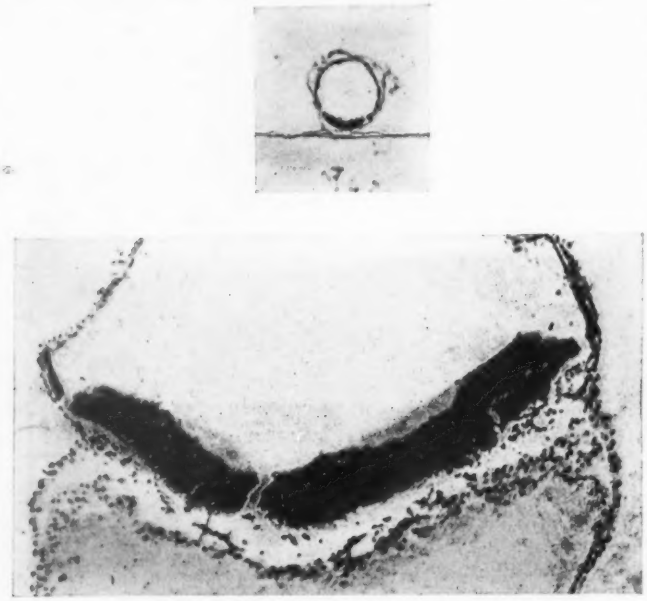

FIG. 4.—Photographs of the twin (above) and the primary embryo (below), taken at the same enlargement (100 diameters) and through similar portions of the embryonic plate.

development. It is probable that under usual conditions the two embryos would be approximately of the same size, and the small size of the twin is to be accounted for by the incompleteness of the bud given off from the primary embryonic node. A comparison of sections made through the amniotic vesicle of the twin and through a corresponding region of the primary embryo, as shown in Fig. 4, would indicate that the former was essentially normal in form though much retarded in development. The complete detachment of the yolk-sac justifies us, however, in considering it as abnormal. If the pregnancy had not terminated in this case it is probable that the larger embryo would have gone on to maturity and the smaller one would have remained stationary in the form of two minute epithelial vesicles and been entirely overlooked.

In closing I would call the particular attention of obstetricians to this point, for it is probable that a careful search at the placental attachment of the umbilical cord would frequently reveal the presence of similar minute epithelial vesicles, the remains of stunted twins. We might thus find that the tendency toward twinning in man is even greater than is now supposed.

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CHANGES IN SKIN SENSITIVENESS TO TUBERCULIN DURING EPIDEMIC INFLUENZA

By ARTHUR L. BLOOMFIELD and JOHN G. MATEER

(From the Medical Clinic of The Johns Hopkins Hospital and University)

The disappearance of the cutaneous tuberculin reaction in measles was systematically studied in 1908 by von Pirquet[1] following an observation of Preisich.[2] Fifty-nine children all failed to show skin sensitiveness during the exanthematic stage of the disease. A few observations made at the time of onset showed that the reaction disappeared for from one to four days before the eruption, to reappear gradually after from the fifth to the tenth day. Von Pirquet lays great stress on the specificity of the absence of the reaction in measles, pointing out that it does not disappear in scarlet fever, epidemic meningitis, typhoid fever or German measles. He associates the phenomenon with the tendency of tuberculosis to become more active after measles and explains it by assuming a disappearance of "ergins"—hypothetical substances which unite with tuberculin in the tissues to produce the reaction. Grüner[3] performed subcutaneous tests in children with measles and showed that with relatively large doses (1 mg.) a reaction could be elicited even during the eruptive stage. He calculated, however, that the skin sensitiveness was reduced about one thousand-fold. The observation of von Pirquet has been confirmed repeatedly in measles, but we have been unable to find reports of any similar constant abolition of tuberculin skin sensitiveness in other acute infectious diseases except during stages of agonal collapse.

During the recent epidemic of influenza we were struck by the remarkably low leucocyte counts encountered even in mild

or ambulatory cases. This suggested that at least some of the reactive processes of the body were in abeyance. It seemed of interest, therefore, to study skin sensitiveness in this disease. The present report deals with the results of cutaneous tuberculin tests in 19 consecutive cases of epidemic influenza studied in The Johns Hopkins Hospital during January and February, 1919. The diagnosis was based on the symptoms, the presence of hyperemic phenomena of the skin and mucous membranes, the character and duration of the febrile reaction, and the leucopenia.[4] It should be emphasized that most of the cases were mild and that the disappearance of the skin reaction was in no way associated with general collapse. Three of the patients developed bronchopneumonia, but all made uneventful recoveries. None of them showed clinical signs of active tuberculosis.

Old tuberculin furnished by the tuberculosis dispensary of the hospital was used. Two drops were placed on the forearm about 5 cm. apart. Linear scarification with a dull scalpel was done through the drops of tuberculin after a control scratch had been made distal to them. The tuberculin was allowed to dry on the arm. The tests were all made by the same observers and read at one-, two- and three-day intervals, the character and extent of the redness and induration being noted. Tests were done during the febrile stage and after the temperature had become normal.

RESULTS

The results of the tests are summarized in Table I. It is apparent that skin sensitiveness to tuberculin was absent in every case but one, both mild and severe, during the febrile stage. During convalescence reactivity returned in 89.4 per cent of the cases, which corresponds to what one would expect in a group of normal individuals of the same age. The return to maximum reactivity was gradual in most cases, as shown by successive tests. In two patients a positive skin test was not obtained during the period of observation, even after the temperature had been normal for from six to eight days.

It should be emphasized that, as in measles, more delicate tests, such as the subcutaneous, would probably show reactivity to be simply depressed and not entirely obliterated, and on this basis the cases may be divided into several groups. In ten of them the first test made during the febrile stage failed to elicit any sign of reaction, whereas during convalescence the test was markedly positive. In six cases in which the temperature became normal on the day on which the test was done, or on the following day, slight grades of reddening and induration appeared about the test scratches. These were regarded as delayed and depressed reactions, inasmuch as all these patients later responded with prompt, strongly positive reactions. It may be that in some of those cases the response was intensified by increased hypersensitiveness following the first test. In one instance of moderately severe typical influenza there was a positive test during the febrile stage. The same degree of reaction was observed in this patient during convalescence.

TABLE I

SUMMARY OF RESULTS OF TUBERCULIN SKIN-TESTS IN EPIDEMIC INFLUENZA

	No.	Per cent.
Total cases studied	19	
Cases giving a positive reaction while fever was present	1	5.2
Cases giving a positive reaction after the febrile stage	17	89.4

Length of time (days) after temperature had become normal before the skin test became positive	Number of cases
1	3
2	4
3	2
4	2
5	3
6	1
11	1

DISCUSSION

Although the literature on alterations of the skin test during acute infectious diseases is meager, it has been generally believed that measles stands out as the only disease in which a constant depression occurs. It is of interest, therefore, to find somewhat similar results in epidemic influenza. Beyond pointing out this fact, it seems difficult to associate the phenomenon in the two diseases, despite certain rather striking analogies which exist between them.[4] It would seem wise, however, to restudy in detail the changes in skin sensitiveness in other acute febrile diseases, inasmuch as similar conditions may perhaps be found to exist.

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NOTE.—Since this article went to press a paper has become accessible (E. Schiffer: Monatschrift für Kinderh., 1918, XV, 189) dealing with the same question. The writer did skin tests on 64 children with "influenza." In 61 the test was negative, in three it was weakly positive. Of 28 reexamined during convalescence, three developed positive tests.

JOHNS HOPKINS HOSPITAL BULLETIN.

The Hospital Bulletin contains details of hospital and dispensary practice, abstracts of papers read and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly. Volume XXX is in progress. The subscription price is $3.00 per year.

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HÆMORRHAGE INTO A POSTSCARLATINAL CERVICAL ABSCESS. LIGATION OF THE COMMON CAROTID. RECOVERY[1]

By T. M. Rivers

On December 1, 1916, E. M., of North Carolina, female, five and a half years of age, vomited and had a slight fever. Two days later, a doctor was called, who found her severely prostrated. A small membrane was seen on the right tonsil and 15,000 units of diphtheria antitoxin were given intramuscularly. On December 5, the patient's temperature rose to 101° F., but was normal or subnormal from that time until her admission to the hospital. Her father developed a sore throat one week after the onset of her illness and a culture from his throat was reported positive for diphtheria bacilli by the bacteriologist of the North Carolina State Board of Health. A culture was not made from the child's throat before admission to the hospital.

About December 5, the cervical glands began to swell. The patient again began to vomit, became stuporous and did not pass urine for 56 hours. After this interval, a small amount of urine was passed which contained a great deal of albumin. Her condition remained about the same until the third week, when a diffuse, dull, red maculo-papular rash appeared, three days before admission. She was considered by her physician to have nephritis following diphtheria and was brought to Baltimore to be admitted to the hospital for that reason.

On admission to the Harriet Lane Home of The Johns Hopkins Hospital, December 23, her temperature was 99° F., pulse 110, respiration 22. The patient was drowsy and emaciated. The tongue was heavily coated. The breath was exceedingly foul. Part of the tonsil, soft palate and posterior pillar on the right side had sloughed, leaving a ragged hole lined with greenish-bud pus. The glands on both sides of the neck were enlarged. On the right side was a mass the size of a lemon, deeply situated below the angle of the jaw on the right side, that was obscurely fluctuating and was obviously an abscess. The liver was two fingerbreadths below the costal margin. Over the body and extremities there was a worm-eaten desquamation. The skin of the palms and the soles was very dry and later desquamated in a way typical of scarlet fever. There was also a diffuse maculo-papular eruption over the body and the extremities which was evidently urticarial in character.

White blood count, 31,000. Blood culture, no growth. Throat culture, negative for diphtheria bacilli, but showed long chains of streptococci. Urine: clear; acid; specific gravity, 1.020; albumin, 3 gm. per liter; sugar, absent; hyaline and granular casts; pus cells, red blood cells and epithelial cells.

Shortly after admission the cervical abscess was opened by means of a small puncture and at least two ounces of pus were obtained from which a hemolytic streptococcus was grown.

The patient seemed to be doing well until 11 p. m., December 26, when she was found in a large pool of blood, exsanguinated, pulseless and gasping for breath. The bleeding had stopped spontaneously and the wound was not disturbed. A subcutaneous injection of 300 c. c. of physiological salt solution was given immediately and within two hours the patient received intravenously 225 c. c. of citrated blood from the mother.

There was another hæmorrhage of about two ounces at 7 a. m. and at 11 a. m. on the following day. At 1 p. m. blood began to spurt from the wound. Dr. Dandy, the resident surgeon, enlarged the incision into the abscess and found an erosion of the lingual and the external carotid arteries and the internal jugular vein and that the hæmorrhage was from these three sources. A ligature was placed around the common carotid and the bleeding from the internal jugular was controlled by packing. The child was greatly exsanguinated and she received a few moments after ligation of the common carotid 150 c. c. of citrated blood which had been kept on ice since the transfusion the night before. After the transfusion she rallied immediately. Her pulse became very irregular, however, and remained so for two weeks. There was sugar in the urine for one week after the operation, but the blood sugar was always normal.

On December 28 her hæmoglobin was 40 per cent (Sahli). An area of erysipelas developed above the wound and spread over the right side of face. On the 29th she again received 200 c. c. of citrated blood. On the 30th her hæmoglobin was 58 per cent (Sahli). Both ear drums were punctured, releasing pus.

On January 1, 1917, another large hæmorrhage took place through the wound. Evidently the ligature on the common carotid had sloughed through. The bleeding, however, was successfully controlled by pressure and the patient again received 150 c. c. of citrated blood. On January 3 her hæmoglobin was 40 per cent (Sahli).

The patient developed generalized œdema, insensibility to pain, waxy flexibility, Chvostek's sign, a double Babinski, exaggerated reflexes, double ankle clonus and a distinct loss of memory for recent events. Gradually she improved. The wound healed slowly under treatment with Dakin's solution. On January 22, an internal strabismus of the right eye appeared, which cleared up in a week. The patient was discharged from the hospital February 2, 1917, well, with normal urinary findings. She has been heard from several times since and continues well.

Adenitis with abscess formation, especially about the neck, is one of the complications of scarlet fever. At times the blood vessels are eroded and severe hæmorrhages take place. The bleeding may come from an opened abscess or it may occur from the ear or through the mouth and nose. Veins and arteries are

[1] From the Department of Pediatrics, The Johns Hopkins University and the Harriet Lane Home of The Johns Hopkins Hospital.

No.	Name	No. Cases	Vessel	Discussion	Autopsy
1	Syme.	1	?	Bled from ear and mouth; 10 days later common carotid ligated, but bleeding continued at intervals for 2½ weeks. Recovery.	
2	Porter.	1	Internal carotid (?)	Blood spurted at times from ear for 4 weeks, resulting in death.	No.
3	Kennedy.	3	Internal jugular (2). 1-?	All died.	2-Yes. 1-No.
4	King.	1	Internal jugular.	Died.	Yes.
5	J. de Bal.	1	Internal jugular.	Died five days after opening of abscess.	Yes.
6	Bloxam.	2	Internal jugular. ?	Died after bleeding five days. Abscess opened and only blood obtained. Later pus discharged from another opening. Recovery.	Yes.
7	Hughes.	1	External carotid.	Bled from abscess cavity 10 days after it was opened. Common carotid ligated, which controlled the hæmorrhage. Child died later.	No.
8	Gordon.	1	Internal jugular.	Died.	Yes.
9	Oshrey.	6	?	Died.	?
10	Blood.	1	?	Died.	?
11	Battersby.	1	?	Died.	?
12	Barret.	1	Internal jugular.	Bled to death through an abscess cavity.	Yes.
13	Mill.	2	Carotid or its branchcs.	One died after bleeding through abscess cavity and through mouth. The other bled to death through the mouth.	No.
14	Dépéret.	1	Internal jugular.	Recovered.	
15	Mondière.	1	Branch internal maxillary artery.	Died.	?
16	Sedgwick.	1	Internal jugular.	Bled to death in three days.	Yes.
17	Brown.	1	Internal jugular.	Bled to death eleven days after abscess cavity was opened.	Yes.
18	Metcalfe.	1	Internal carotid?	Died.	No.
19	McDonald.	1	Internal jugular.	Died.	?
20	Brown.	1	Artery.	Had three large hæmorrhages from mouth.	Yes.
21	Hale.	1	Internal jugular.	Died after bleeding 10 days.	Yes.
22	Nicholls.	1	Internal carotid.	Bled to death in 2 minutes.	Yes.
23	Hymes.	1	Artery?	Bled to death through ear and mouth.	?
24	Hüber.	1	Vein?	Tumor mass on side of neck opened. No pus obtained, but child bled to death. Mass was a hematoma.	?
25	Lovegrove.	1	Artery.	Bled to death in a short time through ear, nose and mouth.	No.
26	West.	1	Branch external carotid.	Vessels of neck laid bare as if by dissection. Died.	?
27	Baader.	3	External carotid. External jugular. Lateral sinus.	All died.	Yes.
28	Hosmer.	1	?	Bled about a pint from between the anterior and posterior pillars on left side of throat. Recovered.	
29	Pepper.	2	Artery.	Bled through mouth. Recovery after ligation of left common carotid.	
			Branch of carotid.	Hæmorrhage controlled by ligation of common carotid. Died.	?
30	Mahomed.	6	?	Two of these same as Pepper reported. Others died.	?
31	May.	2	Internal carotid.	Bled from left ear. Left common carotid ligated. Recovery.	
			Internal carotid?	Bled to death through ear and mouth.	?
32	Hannemüller.	1	Superior thyroid artery.	Bled to death through mouth and nose.	Yes.

involved about equally. Hæmorrhage under such circumstances is very serious and few of the cases recover. Most of the authentic cases on record are tabulated here.

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PUBLICATIONS.

The following eight monographs:

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ANALYSIS OF CEREBROSPINAL FLUIDS OF CATS WITH MENINGEAL INFECTIONS

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During the course of the investigation of experimental meningitis in the cat, sufficient data were collected in this laboratory from analyses of cerebrospinal fluids to warrant the publication of a brief report. Our purpose is not only to present the methods used in routine examination, but to provide standards for possible future research on this same problem. A study of the bacteria virulent within the meninges and of the changes in the cerebrospinal fluid caused by such infections will be found in another publication (Felton and Wegefarth[1]). Our chief interest here lies in the choice and application of methods of analysis of the cerebrospinal fluid of normal and diseased animals.

Meningeal infection has long since been recognized by a cellular and protein exudate in the cerebrospinal fluid. With different bacteria as etiological factors, such pathological conditions within the meninges cause also variations in the concentration of glucose, of sodium chloride and of urea, and perhaps other changes both in inorganic and organic constituents. These latter variations, however, aside from the bacteria, are of more theoretical than practical value for the purpose of diagnosis. Reduced to the simplest possible terms, the increased cellular and protein constituents of the cerebrospinal fluid must be considered for our purpose as giving the clearest indication of a reaction caused by the injection of a known micro-organism into the subarachnoid space.

Inasmuch as the etiology in these experimental meningitides is a known factor and is discussed elsewhere, this phase of the question will be disposed of by giving the procedure employed in routine culturing of the cerebrospinal fluid. Since the organisms virulent for the meninges of the cat were easily cultivated, no special bacteriological technique was required to insure growth. Routinely a double meat infusion 0.5 per cent dextrose broth medium, titrated to between Ph. 7.8 and 8, was used. In making the culture of the cerebrospinal fluid, the operator covered the head of the puncture needle with a small fold of sterile cotton; then after the puncture was made, the stilette, with the cotton pledget still intact, was withdrawn and one to two drops of fluid were allowed to escape. Following the escape of these initial drops, from three to eight drops of the fluid were permitted to fall into the culture tube. The top of the test-tube had been well flamed, the cotton plug was reinserted, and the tube entirely cooled just before use. This simple procedure is cited for the reason that but three contaminations occurred in over 2000 cultures, all these during the experiments on the first one hundred animals. Each inoculated culture tube was incubated for 48 hours and the contents stained. All organisms were identified by appropriate reaction.

The number of white blood corpuscles in the cerebrospinal fluid may be roughly estimated by the turbidity of the fluid. Certainly this is a general rule. In view of the fact that a few red blood cells in an otherwise normal cerebrospinal fluid can easily be mistaken for white cells in a pathological fluid, no specimen was designated turbid without further examination. However, a rather marked difference can be observed in the turbidity caused by red and by white blood cells, respectively. This distinction is brought out in the following manner: When a sample of cerebrospinal fluid containing a few red blood cells (200 to 10,000 per c. mm.) is viewed either by direct or reflected light, it has a velvety appearance. If the tube is twirled, definite cell-eddies with a slight but distinct golden or yellowish sheen can be seen. On the other hand, a cerebrospinal fluid whose turbidity is caused by pus cells, is chalky white and when the tube is shaken, although there are few cell-eddies, the fluid on reflected light is definitely white. Even by these differences in appearance it is not possible, in every case, to distinguish between red and white blood cells. Hence, for accuracy, all fluids were microscopically examined before final classification. This microscopic examination was made in the usual manner. Stained smears were examined for bacteria; cells, stained and unstained, were counted in a double-chambered blood-counting apparatus. A weak solution of toluidin blue proved an excellent stain; this or dilute acetic acid was used.

The methods for the estimation of the protein of the cerebrospinal fluid for experimental work on meningitis leave much to be desired. The well-known clinical tests—those of Pandy, Ross Jones and Noguchi, for example—are at best but roughly quantitative. Though it be granted that they are to some degree quantitative, their strict interpretation depends too largely upon individual judgment. Mestrezat[2] devised a splendid method for protein estimation which consisted in comparing in standard tubes the turbidity, developed in the cerebrospinal fluid by means of a precipitating reagent, with the turbidity prepared from a known amount of protein. This test would be very satisfactory were it not for the difficulty experienced in preparation and preservation of the standards. In another publication, a method which seemed most suitable for our purpose has been described. Since the technique of this has been slightly modified, it becomes necessary to give the details. It is simply a Micro-Esbach, consisting in the precipitation of the protein of 1 c. c. of cerebro-

[1] Felton, L. D., and Wegefarth, P.: The Production of Experimental Meningitis by Direct Inoculation into the Subarachnoid Space. Monograph, Rockefeller Institute, 1919.

[2] Mestrezat, W.: Le liquide céphalo-rachidien, normal et pathologique. Paris, 1912.

spinal fluid in a small graduated tube by means of 0.8 c. c. of Tsuchiya's reagent. The tubes are 4 to 4.5 mm. in diameter and 250 mm. long. The graduations range from 0.5 to 5 gm. to a liter. The tubes were standardized in the following manner: Human serum was diluted with Locke's solution and made to correspond roughly to the percentages desired as measured in a Esbach. This determination was finally corrected by a refractometric estimation. In the small tube to be graduated, each of the protein solutions was precipitated three times and the average level of the precipitation taken to indicate the percentage of that standard solution. Precipitation was allowed to continue for 24 hours before reading. Later in our work the Paca Glass Company of Baltimore prepared, from our standards, tubes on which was marked the height for the cerebrospinal fluid and for the precipitating reagent, in a way similar to that employed for the Esbach.

In the routine estimation of protein, the following technique was employed: By means of a capillary pipette the cerebrospinal fluid is allowed to run into the tube to the mark "Spinal Fluid." Similarly, Tsuchiya's reagent is added to the "reagent" mark. A cork is inserted and the tube gently turned over 10 times, thus causing the bubble of air to thoroughly mix the reagent and spinal fluid, as well as to break up any large clumps of precipitate. The tube is then placed in an exactly vertical position for 24 hours. Precipitation will not be complete if too much protein be present or if the tube be dirty. The best results are always obtained by diluting with normal saline very turbid fluid to one and one-half or more times its volume before putting it into the precipitometer. The tubes are cleaned by inserting a capillary pipette to the bottom of the tube and forcing water through the pipette until all the precipitate has been washed out. Then, with a swab, made by wrapping a bit of absorbent cotton on a small wire, the tube is dried.

Although in this procedure a day elapses before the final reading, this delay is no real disadvantage, for one may as correctly judge the approximate quantity of protein by the number of flocculi produced immediately after the mixing of the Tsuchiya's reagent and cerebrospinal fluid, as by the degree of turbidity developed in the Pandy and Ross-Jones test. In addition, one may have at the end of 24 hours a comparatively accurate idea of the protein-content of the fluid examined. Although an exact estimation of the protein-content of the cerebrospinal fluid is not claimed for this method which gives perhaps an error of 25 per cent, it has proven useful in this series of experiments.

Since Felton [3] has shown that Lange's colloidal gold test is possibly an estimation of the albumin-globulin content of the cerebrospinal fluid, rather than a specific reaction for any one lesion of the nervous system, it was thought advisable to employ the test both as a check upon the protein-content and for the purpose of gaining possible information concerning its specificity. The action was carried out in the classical way, the gold sol being prepared by a slight modification of Lange's method.[4] The solution was neutral to alizarin red; 5 c. c. were precipitated by 2.7 c. c. of a 1 per cent solution of sodium chloride; a cerebrospinal fluid from a patient with general paresis gave a typical paretic curve. Each preparation of the solution was also standardized by means of a sample of serum globulin, that is, the globulin solution diluted in Locke's solution until 0.2 c. c. run in the regular test caused a reaction in the paretic zone. This globulin solution was then kept in the ice-box and was utilized to check the sensibility of the sol.

In order that correct conclusions may be drawn in regard to meningeal infection, as it is manifested in the cerebrospinal fluid, the analysis of the normal fluid of the cat must be known. Macroscopically the cerebrospinal fluid of a cat, not differing from that of any other mammal, is a colorless limpid fluid. Microscopically, however, there are a few white blood corpuscles, perhaps 0 to 10 to a c. mm., and occasionally a number of red blood cells.

TABLE I.—NORMAL SPINAL FLUIDS

Animal	Date	Character of fluid	C. c. of fluid	R. B. C. per c. mm.	W. B. C. per c. mm.	Protein grams per liter	Gold sol.
456	4- 5-18	Clear	1.5	3	0	0.4	0000111100
449	3-28-18	Clear	1.5	40	10	0.2	0000111000
574	5- 8-18	Clear	1.5	20	10	0.6	1122100000
576	5- 8-18	Clear	1.0	10	10	0.5	1122100000
582	5- 9-18	Clear	1.0	50	10	0.5	1110000000
654	5-24-18	Clear	1.0	0	10	0.15	1222100000
830	6-28-18	Clear	1.0	0	10	0.4	0000000000
715	6-10-18	Clear	1.5	0	0	0.6	0001100000
716	6-10-18	Clear	1.0	0	10	0.3	0110000000
722	6-11-18	Clear	1.5	10	0	0.5	1110000000
758	6-17-18	Clear	1.0	10	0	0.4	0000000000
831	6-23-18	Clear	×	0	5	0.3	0100000000
755	6-17-18	Clear	2.0	0	10	0.5	1110000000
746	6-15-18	Clear	1.0	0	10	0.5	1110000000
881	7- 5-18	Clear	1.5	2	0	×	0011100000
464	4- 2-18	Clear	1.5	0	0	0.3	0011000000
674	5-27-18	Clear	1.5	30	20	0.1	1123311000
543	5-29-18	Clear	1.0	5	0	0.5	1110000000
571	3- 7-18	Clear	1.5	29	10	0.4	0011000000
757	6-17-18	Clear	1.0	10	10	0.1	0011100000
596	5-14-18	Clear	1.0	10	0	0.5	4553221000

From Table I, one would judge that the cellular element was rather variable, white corpuscles 0 to 20 and red 0 to 50 a c. mm. This table represents the average cerebrospinal fluid of normal cats contained in routine daily occipito-atlantoid punctures rather than the description of the exactly normal fluid. That there are no erythrocytes in the cerebrospinal fluid from normal cats has been demonstrated by the examination of a great number of fluids.

The protein-content varies from 0.1 to 0.6 gm. to a liter. This is rather remarkable and does not accord with the constant amount found to be present in normal human cerebrospinal fluid by Mestrezat,[5] and later by Felton [3]—0.25 gm. to a liter. Although we have had a few fluids in which no protein could be demonstrated, a great majority have sufficient to give a precipitate equivalent to between 0.25 and 0.5 gm. to a liter. We consider 0.25 gm. as a low normal and 0.5 gm. as high, bordering on a pathological fluid.

The colloidal gold reaction of these fluids as a rule shows a normal curve. The records from Cats 674 and 596 were exceptions, for in these the cellular and protein elements were

[3] Felton, L. D.: A Study of the Specificity of the Colloidal Gold Reaction from the Physico-Chemical Standpoint. Trans. A. M. A., Sec. on Path. & Physiol., 1917, 73.

normal; one a reaction in the luetic zone and the other in the paretic. Our only explanation is that the animals, although they appeared perfectly normal, may have had chronic lesions in the meninges.

The cases of acute meningitis are arbitrarily divided into two classes because of a more complete fluid analysis in one group of animals than in the other. Table II represents a

TABLE II—ACUTE MENINGITIS.

	No.	Date	Character of fluid	Amount	Cells	Protein	Gold sol reaction
Intravenous injection, 3/14, of B. lactis aërogenes and withdrawal of spinal fluid. Animal died on 3d day.	400	3/14	Clear	1.0	0	5.0	0221000000
	400	3/15	Turbid	.5	14400	60.0	4455553000
Same as 400 except .25 c. c. organisms was given intravenously on 3/15. Animal died on 3d day.	412	3/15	Clear	1.0	0	5.0	0011100000
	412	3/16	Turbid	2.0	1400	6.5	0112344444
Same as 412, injection on 3/17. Animal died on 5th day.	417	3/17	Clear	1.5	....	....	0111000000
	417	3/18	Turbid	.5	100,000	7.0	0125555555
Subarachnoid injection 2 c. c., 24-hr. dialyzate of B. lactis aërogenes on 6/10.	715	6/10	Clear	1.5	0	.6	0111000000
	715	6/11	Turbid	1.0	6000	13.0	5554321000
Subarachnoid injection of 2 c. c. of a 65-hr. dialyzate of B. lactis aërogenes on 6/17.	753	6/17	Clear	1.5	10	.2	0000000000
	753	6/18	Turbid	2.0	224,000	4.9	0554443333

well-controlled experiment, both the normal and pathological conditions being present; whereas in Table III the fluids were subjected to at least one characteristic test and found to be normal. It is very probable that the analyses in one group of animals is as trustworthy as in the other. As indicated in Table II, acute meningitis of the cat is accompanied by definite changes in the cerebrospinal fluid; it is turbid, a great number of pus cells are present, the protein-content is increased, and the gold sol reaction denotes abnormality. Cats 411, 412 and 417 were typical clinical cases of acute meningitis—hypersensitive, ataxic, spontaneously crying out as if in pain, and developing acute convulsions on retraction of the head. Animals 715 and 753 were normal on the day following the injection, though possibly a little weak in the hind legs, and at the time of puncture they did not show a clinical meningitis. The first group of animals died and when autopsied were found to have well-marked leptomeningitis; the latter group remained to all appearances normal. From the standpoint of fluid-analysis, the five animals in Table II had definite infective processes in the subarachnoid space. The gold sol reaction of the fluid is interesting. Though all the other findings in the cerebrospinal fluids denoted acute inflammation of the meninges, three of the five produced reactions in the paretic zone. The divergence from the general rule cannot easily be explained. It may be possible that the protein-content in an abnormal cerebrospinal fluid of a cat differs from the human and that there is a relative increase of globulin over the albumin. This last statement has been made in the light of previous work on the explanation of the colloidal gold reaction (Felton[3]). It was found that the precipitating factor in the cerebrospinal fluid, if not the globulin itself, was intimately associated with the globulin, in contradistinction to the albumin; this latter as a negative sol neutralizes the precipitating power of the globulin. The interrelationship of these two substances or proteins, produces the zones in the reactions. If this be true, it is highly probable that in Cats 400, 715 and 753 we are dealing with cerebrospinal fluids containing a greater proportionate amount of globulin over the albumin than in those of Cats 412 and 417.

TABLE III.—ACUTE MENINGITIS

Animal	Character of fluid	Cells	Protein	Gold sol reaction	Injection
350	Turbid	1400	0.9	1234553411	Spontaneous meningitis.
420	Turbid	2840	5.0	1123354444	Intravenous mucosus capsulatus and lumbar puncture.
256	Turbid	10000	11.0	0012234433	Subarachnoid, Behring B. coli.
665	Turbid	170	1.4	12455431006	c. c. mucosus capsulatus Berkefeld filtrate. Subarachnoid.
758	Turbid	8000	5.5	1112343333	24-hour mucosus capsulatus dialyzate.
774	Turbid	....	2.2	1112333211	24-hour mucosus capsulatus dialyzate.
270	Turbid	9080	4.0	1233210000	Subarachnoid mucosus capsulatus, 1-12,000.
252	Turbid	9000	9.0	0111244321	Subarachnoid mucosus capsulatus, 1-15,000.
253	Turbid	1800	2.0	0000123210	Subarachnoid mucosus capsulatus, 1-10,000.
254	Turbid	....	....	0011244321	Subarachnoid mucosus capsulatus, 1-10,000.
285	Turbid	....	5.0	0012344321	Subarachnoid mucosus capsulatus, 1-250,000.
596	Turbid	200	4.0	1335555555	Intravenous mucosus capsulatus, occipito-atlantoid puncture.
417	Turbid	100,000	6.0	0123555555	Intravenous mucosus capsulatus, occipito-atlantoid puncture.
684	Turbid	1000	2.0	2455332110	Mucosus capsulatus, Berkefeld filtrate, 72 hours.
755	Turbid	....	2.0	1112355532	Mucosus capsulatus, Berkefeld filtrate, 24 hours.
764	Turbid	7160	4.5	1113444332	Mucosus capsulatus, Berkefeld filtrate, 72 hours.

All of these animals (Table III) were given direct subarachnoid injections with micro-organisms or with filtrates or dialyzates prepared in one way or another from micro-organisms. And although most of the animals developed an acute and fatal meningitis, confirmed at necropsy, a number not only survived, but were not noticeably affected. Nevertheless, in view of the reaction of the meninges as evidenced in the cerebrospinal fluid, all can be classified as cases of acute meningitis. The gold sol test in this group of cases is not so atypical as in the former group—the reaction taking place more characteristically in the meningitic zone. However, in animal 270 the gold sol reaction was exhibited in the luetic zone. Comparing Lange's test in the two groups of acute meningitides, it is evident that the cerebrospinal fluid of animals having acute meningitis does not cause a differential zone reaction, the curves occurring in any of the three regular zones.

The cerebrospinal fluid of a cat having chronic meningitis varies only slightly from the fluids obtained in that disease in the human subject. As can be seen from Table IV the character of the cerebrospinal fluid changes from turbid in the acute or subacute stage of the disease to clear in the definitely chronic condition. The number of pus cells and the amount of protein vary in about the same relation—a gradual decrease in both elements. The gold sol reaction is very remarkable.

In the acute stage of the disease the cerebrospinal fluid exhibits the average reaction with all the tests for that condition. But with one exception (293) the gold sol reaction takes place in the paretic zone. For instance, Cat 211

with a turbid fluid, containing 800 pus cells, 10 grams of protein to a liter and giving a reaction in the meningitic zone with the gold sol test, was sick for over two months (finally sacrificed because of its weakness) and a month before death the cerebrospinal fluid was normal except for three (blue) reactions in the paretic zone with Lange's test. Better

TABLE IV.—CHRONIC MENINGITIS

Clinical course of animal	No. of animal	Date	Character of fluid	Cells	Protein	Gold sol reaction
Subarachnoid injection of 1 c. c. Streptococcus mucosus on 12/27. For 3 days cat seemed normal. On 12/31, a little drowsy and weak; refused to eat up to 1/5 when it began to take food and was practically normal 1/9. Animal was transferred 3/6. Culture of spinal fluid was negative throughout.	105 B	12/27	Clear	0	..	0011110000
		1/29	Clear	80	.3	1233210000
		2/22	Clear	..	.5	2333210000
		3/ 6	Clear	21	.2	2333210000
Subarachnoid injection of 1 c. c. 1–10, B. coli, No. 9, 1/24 normal active animal throughout the entire period of observation. Positive culture of spinal fluid 1/29 and 2/4; negative 2/19.	4-5	1/29	Turbid	..	3.0	0012345555
		2/ 4	Turbid	..	..	0012345555
		2/ 7	Solution turbid	40	.8	0123321000
		2/19		..	.5	3443210000
2/8. Subarachnoid injection of 2 c. c. cat streptococcus. Down on side and sick for 2 days; gradually improved, but continued somewhat weak up to 2/21. Cultures of spinal fluid 2/11 negative.	169	2/ 8	Clear	..	.5	0011100000
		2/11	Turbid	..	1.5	0013331000
		2/21	Turbid	512	.8	2344321000
2/27. Subarachnoid injection of streptococcus from autopsy No. 3458. C t was acutely ill and developed chronic state represented by refusal to eat, ataxic gait. Sacrificed with ether 3/21. Little evidence macroscopically of meningitis. Dura lost its luster. Markings in cord indistinct.	328	2/28	Turbid	2200	2.5	3334221000
		3/ 1	Turbid	540	2.0	1124432100
		3/16	Solution	90	.8	0123321000
		3/21	turbid	20	.3	3332100000
			Clear			
Subarachnoid injection of cat streptococcus 1/29. Quite weak the next day. The cat became thinner, weaker, and more ataxic up to its death 4/16. (Sacrificed with ether). 2/5. Culture was positive for streptococcus, negative afterward.	311	1/30	Turbid	800	10.0	0012344444
		2/ 5	Turbid	..	5.0	0024555555
		2/ 8	Turbid	400	1.0	.....
		3/ 8	Clear	..	0.2	3332100000
Subarachnoid injection of pneumococcus 2/19. Cat was quite sick for 7 or 8 days. Became active and normal 3/5.	293	2/25	Turbid	1440	0.0	5553210000
		3/ 5	Clear	90	..	1243210000
After subarachnoid injection of B. typhosus 12/31, developed very marked acute meningitis changing into subacute and chronic in 2 months. Sacrificed 4/21. Autopsy showed chronic process over hemispheres.	124	2/11	Clear	40	.3	4443210000
Chronic pneumococcus meningitis 21/2 months.	107	1/29	Clear	90	.6	3444221000
		3/ 6	Clear	..	.2	3444321000
Acute streptococcus meningitis for 10 days, then normal active animal from 2/22 to 3/11.	300	3/ 6	Clear	..	.4	3553200000
Subacute meningitis at autopsy. B. gallinarum 1 month's duration.	134	2/ 4	Clear	214	.8	5555532100
Subarachnoid injection 1 c. c. 1–400 B. coli, Behring, 2/25. Acute meningitis over period of a week. Normal active animal after 8 days.	310	3/12	Clear	..	.6	5555321000
Subarachnoid injection 3/1. 1 c. c. 1–400 B. coli, Behring. Normal active animal after 8 days.	315	3/21	Clear	..	.2	3332100000

examples of this change are found in Cats 134 and 310. Each of these, though examined but once, show a cerebrospinal fluid that is almost typical of the one found in general paresis—a clear fluid, having 214 cells, with a slight increase in the protein-content and an exact representation of a paretic zone reaction. Possibly our best clinical example of chronicity is Animal 124, which showed at necropsy a typical chronic meningitis. For two days after the initial subarachnoid injection of 1 c. c. of a 24-hour broth culture of *B. typhosus*, the animal was drowsy, had a wobbly gait, reacted as if to pain on retraction of head, and refused to eat. Unfortunately there were too many erythrocytes present in every cerebrospinal fluid obtained, except the one given in Table IV, to make a complete record. *B. typhosus* continued to be present in the cerebrospinal fluid for one month as determined by cultures. Clinically, the drowsiness gradually cleared up, the animal's appetite returned slowly, but it remained sick. The gait changed from an ataxia to an almost complete paralysis of the hind legs. Its condition became progressively worse so that it was sacrificed at the end of two months. The heart's blood and cerebrospinal fluid cultures were negative at necropsy. A similar case, but with complete cerebrospinal fluid analysis, is found in Animal 328. Were it not for the clinical picture of an acute onset developing into a chronic state (weakness, loss of appetite, ataxic gait, etc.) one would be justified in diagnosing the case as a normal recovery from an acute meningitis. A culture of the cerebrospinal fluid was negative on the sixteenth day.

The reversal of the zone reaction of the Lange's test parallel to the development of a chronic state in the animal is of more than passing interest. We have an acute irritation of the meninges with a characteristic exudate (Animals 328, 211, 169) slowly subsiding and becoming, as far as we are able to tell from the cerebrospinal fluid, almost normal. Accompanying this is a gradual decrease in the precipitating factor of the spinal fluid in the colloidal gold test with a change from a meningitic to a paretic reaction. Many possibilities suggest themselves in explanation. Granting that the precipitating agent of the cerebrospinal fluid is globulin, the question as to the source of this protein naturally arises. Are we dealing with a residual globulin from the acute inflammation of the meninges; have the meninges so changed in character that albumin is allowed to pass and globulin is not (a thing that is not possible *in vitro* when a dialyzing sack is used); is the globulin of the central nervous system thrown into solution in a process of gradual degeneration; or do the micro-organisms synthesize a globulin by their growth?

The similarity of the zone reaction in chronic meningitis of the cat to the reaction given in general paresis in man leads us to ask whether the cerebrospinal fluid of any chronic lesion of the nervous system will produce a paretic curve. That this occurs in some cases, at least, of multiple sclerosis, brain abscess, chronic lead poisoning and paralysis agitans, is well known. It is probable that other chronic diseases of the central nervous system will cause a reaction in the paretic zone, if the examination be made at the proper time. It is not our purpose to belittle the value of the test in general paresis provided the Wassermann reaction be done at the same time, but the importance of care in interpreting reactions of the paretic zone should be emphasized.

SUMMARY AND CONCLUSIONS

I. A method is given for the measurement of protein in the cerebrospinal fluid. It has been found to be of as great value in acute meningeal infections as the Pandy or Ross Jones tests in

differentiating the cerebrospinal fluid of normal cats from those with chronic lesions in the central nervous system.

II. The normal cerebrospinal fluid of a cat contains 0 to 10 white blood corpuscles per cubic millimeter, from 0.1 to 0.5 gm. of protein to a liter, and gives a negative curve in the colloidal gold reaction.

III. The cerebrospinal fluid in acute meningitis of a cat has been found to contain from 200 to 22,400 white blood corpuscles, 2 to 17 gm. of protein to a liter, and to given a reaction in any of the three zones in the gold sol test.

IV. The cerebrospinal fluid of chronic meningitis of a cat is practically normal with exception of the gold sol reaction, a change to the paretic or to the luetic zones has been recorded. There may be a slight increase in the number of white blood corpuscles and in the content of protein.

V. The colloidal gold reaction has been of service in demonstrating a pathological cerebrospinal fluid, but has shown no specific zone reaction, except to a slight extent in the cerebrospinal fluids from animals with chronic meningitis.

VI. There was indeed a great similarity in the Lange's test as applied to the cerebrospinal fluids from cases of experimental chronic meningitis, and those of general paresis in human patients. It was suggested that the paretic zone or even the luetic zone reaction denotes, where there is a small amount of protein present, merely a chronic lesion of the central nervous system.

HORACE GREEN AND HIS PROBANG[1]

By William Snow Miller,
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One of the interesting episodes connected with the history of American medicine is associated with the name of Horace Green who, in 1840, announced that he was able to pass a sponge-tipped probang into the larynx and thus apply medication directly to the laryngeal mucosa, and even to that of the trachea. The stormy discussion occasioned by this simple statement extended over a period of 19 years and spread beyond this country to England and France.

Horace Green was born in Chittenden, Vermont, December 24, 1802, and died at his home at Sing Sing, now Ossining, New York, November 29, 1866, in the sixty-fourth year of his age. His father was one of four brothers, sons of a Massachusetts physician, who served in the Revolutionary War. Two of them fell with Warren at the battle of Bunker Hill; the third fell in the battle at Monmouth; the fourth fought through nearly the whole of the long struggle and raised four sons, the youngest of whom is the subject of this sketch.

Horace Green studied medicine with his brother Dr. Joel Green, of Rutland, Vermont, and graduated at Middlebury, Vermont, in 1824, from the institution known later as the Castleton Medical College. The succeeding five years he spent in partnership with his brother, and in the fall of 1830 went to Philadelphia where he attended lectures at the medical department of the University of Pennsylvania. In the spring of 1831 he returned to Rutland where he continued in practice until 1835 when he removed to New York City.

In 1838 he spent some months in Europe, and on his return, late in the year, began at once his investigations into the pathology and treatment of diseases of the throat.

From 1840 to 1843 he was connected with Castleton Medical College as professor of medicine and as president of the institution. In 1850 he helped to found the New York Medical College. Here he occupied the chair of theory and practice of medicine and was elected president of the faculty and also of the board of trustees. In 1860 he retired from active service and was made emeritus professor. In 1854 he, and his colleagues, founded the American Medical Monthly. Dr. Green was A. M. (honorary) from Union College; LL. D. from the University of Vermont; Phi Beta Kappa and a member of the Society of the Cincinnati.

In the Boston Medical and Surgical Journal, Volume XLII, 1850, a good pen picture is given of Dr. Green. He is described "as tall and rather spare; very black hair, now a little grey; a sharp black eye, rather a brunette; and gentle and kind in his address. His manners are quiet and dignified, those of a gentleman accustomed to good society. They say a poet must be born. Cato [*nom de plume* of the author] opines that this is equally true of a gentleman; and he further thinks that nothing so deforms a man, especially a medical man, as rough or clownish manners. If any man should be gentle, in the highest sense of the word, it is he who ministers to our diseased bodies and minds." The account closes "long may he live to enjoy the honors and emoluments of the profession which he has well and truly labored in."

In the obituary notice of Dr. Green published in the New York Medical Journal, Volume IV, 1886, it is stated: "Few men in the profession of medicine in this country have attracted so much attention to their professional career as did Dr. Green. Announcing, in his earlier writings, a plan of treatment for diseases of the air passages which was at once regarded as 'bold and novel,' it met, naturally, much skepticism and opposition. This induced investigation into the subject in dispute. An impetus was given to the study of laryngeal diseases, and, as a result, the means of their diagnosis and treatment have been immeasurably increased. Dr. Green lived to see the views he promulgated thoroughly proved by the aid modern science has placed in our hands."

Horace Green published his "Treatise on Diseases of the Air Passages" in 1846. In the introduction to this work he says: "More than six years ago, namely, in 1840, I brought before the New York Medical and Surgical Society, ...

[1] Read before the Wisconsin Medical History Seminary, 1916-1917 session. Read before the Historical Club of The Johns Hopkins Hospital, May 26, 1919.

HORACE GREEN.

Enlarged from a small card photograph in the Howard A. Kelly collection of portraits at the Johns Hopkins Hospital. This was taken probably about 1855.

the subject of the treatment of diseases of the larynx, by direct application of therapeutical agents to the lining membrane of that cavity. . . . . Such, however, was the degree of skepticism on this subject, manifested, at the time, by a large proportion of the members, that for many years I have refrained from bringing the matter again before the society."

The first three chapters of the book deal with the anatomy and pathology of the throat, larynx and bronchi. In the fourth chapter the main purpose of the book is stated when emphasis is laid on the mucous glands and follicles "scattered along the extent of the lining membrane of the respiratory tubes." When these are affected they give rise to that affection of the throat which is called "bronchitis"; "chronic laryngitis"; "clergymen's sore throat," and is frequently found among public speakers and others. "The structural changes, to which the mucous follicles of the throat and air passages are liable, are: Inflammation, which may result in ulceration, hypertrophy, induration, or in a deposition of tuberculous matter in the follicles themselves; attended, in most of these conditions, by a greatly increased, and vitiated, mucous secretion."

"The disease of the mucous glandulæ may be primary, and uncomplicated, and be limited, entirely, to the fauces and pharyngo-laryngeal membrane; or, it may be complicated with hypertrophy, and induration of the tonsils, and with elongation of the uvula. It may accompany, or be consecutive to, other affections of the air passages, and co-exist with laryngitis, bronchitis, or with pulmonary phthisis."

Among the causes of "follicular diseases" or, as we now term it "follicular pharyngitis" or "granular pharyngitis," Green enumerated climate, age, influenza, sudden strain of the voice in public speaking and tobacco. Valentine Mott, on his return from his European trip, said that the reason why clergymen on the other side of the water were so free from "sore throat" was their free use of "the weed." I am afraid I shall have to agree with Mott. The assignment of influenza as an exciting cause is, I think, agreed to by most of us from personal experience.

I pass over much that is of interest in the volume, mentioning only his illustration of œdema of the uvula which occurred in a case where suffocation was nearly caused, in two instances, by its being aspirated into the glottis, and take up Green's method of treatment. He did not neglect constitutional remedies when he considered them serviceable; his chief method of treatment was, however, the application, by means of a sponge-tipped probang, of a solution of silver nitrate, which varied in strength from two to four drachms of the crystals to the ounce of distilled water. He lays emphasis on the use of the solution of the pure crystals rather than the solid nitrate. In some cases where extensive ulceration was present he did not hesitate to apply a solution of double the last-mentioned strength. The silver, he says, "does not act, as has been supposed, by burning, or by destruction of tectural matter: it forms, immediately an union with the albumen, and other secretions of the mucous lining, and this compound, thus formed, defends the living tissue from the action of the caustic; whilst it operates to produce a most favorable change, in the vital actions of the parts."

Green laid a great deal of stress on the proper education of the larynx in order that the probang could be properly, and with as little difficulty as possible, introduced into it. Disregard of this point caused numerous failures, as we shall see later, by the committee who investigated his method of treatment. The larynx should not be entered at the first sitting, but the solution should be applied about the epiglottis and pharyngeal region on several successive days before this is attempted (this was before the days of cocaine).

The directions for passing the probang are explicit. "The instrument being prepared, and the patient's mouth open wide, and his tongue depressed; the sponge is dipped into the solution to be applied, and being carried over the top of the epiglottis, and on the laryngeal face of this cartilage, is suddenly pressed downwards and forwards, through the aperture of the glottis, into the laryngeal cavity" (the laryngoscope had not as yet come into use).

The year following the publication of Dr. Green's work on "Diseases of the Air Passages" there appeared in the Boston Medical and Surgical Journal a most bitter and, as later events showed, unwarranted attack on Dr. Green and his book. The book is designated as "a misnomer, for nothing whatever either novel, important or useful, is even suggested in relation to 'bronchitis.' The whole ten chapters are made up of a dissertation upon follicular disease." The reader "will expect to find the proofs that the novel feat of passing an armed probang, through the larynx, into the trachea down to the bifurcation, has been performed, thus curing bronchitis by the topical application of his curative means to the inflamed membrane. It is this monstrous assumption which was scouted by the profession, as 'ludicrously absurd, and physically impossible.'"

The author of the article in question states that in all probability the armed probang entered the œsophagus and on its withdrawal some of the contents of the sponge "has descended into the laryngeal cavity." The article goes on to say "he has the name of having accomplished, what the profession declared to be impossible, by swabbing out the larynx, trachea and bronchi themselves."

But the author brings a still more serious charge against Dr. Green—plagiarism. Trousseau and Belloc published in Paris, in 1837, a work entitled "Traité pratique de la phthisie laryngée." This was translated into English and published in Philadelphia in 1839; this is the work that Green is charged with plagiarizing. Green had affirmed that he had been using his method of treatment for two years before he heard of Trousseau and Belloc; but the author scorns his statement saying that as Green was in London in 1838, it was impossible for him not to have heard of Trousseau and Belloc.

Let us see what Trousseau and Belloc have to say on the subject and if they really did enter the larynx for the direct application of medication. They first describe the bending of a piece of whalebone and the tying on of a small piece of sponge which they moisten with a solution of nitrate of silver. With

the mouth open, and the tongue depressed, they introduce the armed probang. "When the isthmus of the gullet is passed, there occurs an effort of deglutition which elevates the larynx, and we seize this opportunity to draw forward the sponge, which had been at the entrance of the œsophagus. By this manœuvre we get the glottis, and it is easy to express the solution into the larynx; the cough which now occurs favors the introduction of the caustic." This is quite another thing from entering the larynx and applying medications directly to the parts as Green claimed to do; moreover, Trousseau later was exceedingly skeptical of the assertion made by Green that the larynx could be entered, but finally, in 1858, he acknowledged that Green had actually accomplished this feat. The relation between the two men was always a pleasant one and we find Trousseau sending patients to Green for treatment.

An extended review of Green's book is also found in the New York Journal of Medicine, Volume VIII, 1847, in which Green is highly complimented for the work he has accomplished and the advance he has made in the treatment of laryngeal affections, but the reviewer fails to distinguish between the expression of medication from a sponge-tipped probang and the passage of a sponge-tipped probang into the larynx thus applying the medication directly to the mucosa.

In 1851 Green returned from a second visit to Europe and we now find that the discussion of his method of treatment has extended to the other side of the Atlantic, for Erichsen, in his "Science and Art of Surgery," London, 1853, declares that "Not only does physiology and ordinary experience tend to disprove the possibility of such a procedure, but repeated experiments, both on the living and on dead subjects, have led me to the conclusion that it is utterly impossible to pass a whalebone, whether curved or straight, armed with a sponge, beyond, or even between, the true vocal chords."

On the evening of December 6, 1854, Green read before the New York Academy of Medicine a paper entitled "On the Employment of Injections Into the Bronchial Tubes, and Into Tubercular Cavities of the Lung." In this paper Green reviews the work he has accomplished and gives additional cases which have been successfully treated. He also mentions by name numerous well-known physicians who had used his method successfully. Marshall Hall, an eminent physiologist of his day, about this time was on a visit to this country and the scene for the moment shifts to Chicago. Like Erichsen, Marshall Hall believed that the introduction of "a sponge wet with the caustic solution into the larynx and trachea, as proposed, would prove fatal to animal life." He was won over to Green's support by seeing Professor Brainard introduce a tube into the trachea of a dog, and afterwards by seeing Green perform the operation of cauterizing the larynx and trachea at his office in New York. Marshall Hall's renunciation of his former position can be found in the Northwestern Medical and Surgical Journal, Volume II, N. S.

It was Marshall Hall who suggested to Green the use of a tube and the passage out of it of the expired air as a proof of tracheal catheterization. Green accordingly procured a number of Hutchings' flexible tubes and attaching a sponge, the size of that used by him in ordinary practice, to the extremity of one which was 13 inches long he introduced it into the trachea of a patient.

"On withdrawing the wire the patient was directed to blow and breathe through the tube. This he did for several moments filling and emptying the chest of air repeatedly. A lighted lamp was then brought, and this was extinguished promptly, several times, by blowing through the tube." In still another test a bladder was tied to the free end of the tube and it was inflated and collapsed a dozen times. These and numerous other experiments are described by Green in his paper to prove that he was able to enter the larynx for the direct application of medication.

The paper is lengthy and I cannot improve on the summary given by Fordyce Barker in his report to the New York Academy of Medicine. He states that Dr. Green's paper contains the following three distinct propositions:

1st. That direct medication of the lungs, by means of catheterism of the air tubes, has not before been accomplished.

2d. That the operation may be performed by the dexterous surgeon with ease and facility, and with perfect safety to the patient.

3d. That the results of this method of treating disease, whether it is employed in bronchial affections or in the commencement of tuberculosis, have already afforded the most gratifying indications that practical medicine will be advanced by this discovery.

A committee of seven was appointed by the academy to "investigate the treatment proposed by Dr. Green in his paper read this evening." The committee consisted of Drs. Willard Parker, chairman; Isaac Wood; James Anderson; John O. Stone; B. Fordyce Barker and J. T. Metcalf. After a delay of six months this committee reported Wednesday evening, July 18, 1855. Two reports were submitted; a majority report signed by Drs. Parker, Stone, Wood and Metcalf. The minority report was submitted by Dr. B. Fordyce Barker. Drs. Anderson and Stevens did not sign either report, but sent letters to Dr. Parker, the chairman, stating that they did not think the committee had given sufficient investigation to some of the features of the report or that they were not fully convinced in regard to the practicability of introducing the probang into the trachea. The conclusions of the majority report are as follows:

1. Catheterism of the air-passages dates its history from the time of Hippocrates.

2. The best evidence of the presence of an instrument into the air-passages are the rational signs.

3. The facility of the operation depends upon the kind of instrument used; the tube having a large curve being the best, and the sponge probang least adapted to enter the trachea.

4. That there is no reliable evidence, in the opinion of your committee, that the sponge probang has been passed through and beyond the vocal chords.

5. That there is no positive evidence that an instrument can be passed at will into the right or left bronchial divisions.

6. That, in the great majority of instances, where injections are supposed to have been thrown into the lungs through a tube, they have passed directly into the stomach.

7. That, as regards the utility of injections of nitrate of silver into the lungs, the facts thus far developed in the experiments of

your committee lead them to regard the operation as one attended with danger as well as difficulty.

The minority report sets forth the duties of the committee as follows:

1st. To ascertain whether direct medication of the lungs, by means of catheterism of the air tubes, has been before accomplished.

2d. To ascertain whether the operation may be performed by the dexterous surgeon with ease and facility, and with perfect safety to the patient.

3d. To ascertain, as far as possible, the therapeutic results of this treatment.

The following extract from the records of the secretary of the committee is quoted in support of this position:

It was concluded, after some general discussion of the subject, that the committee should endeavor, first, to settle the question of the passage of the tube into the trachea; and as far as possible, to ascertain the utility of the injections of nitrate of silver into the lungs.

Although Dr. Green insisted that the throat should be properly educated before attempting to pass the probang, the committee disregarded the purpose for which they had been appointed and spent a considerable amount of time in attempting to pass the sponge probang without any previous preparation of the patient and in a very crude manner, as will appear later. Dr. Green himself failed to pass the instrument in some cases, when the committee requested him to make the attempt, from this very cause; but in one instance in which he passed one probang into the trachea and a second one into the œsophagus, moving the one in the œsophagus up and down produced no motion by the first; nevertheless, Dr. Parker was not convinced that the first was in the trachea.

The statement made by the majority report that "catheterism of the air passages dates from the time of Hippocrates" was called in question by Dr. Barker and it may still be called in question by the student of medical history.

The full minority report, like the majority report, was lengthy, and I will give the conclusions presented to the academy:

1st. Direct medication of the lungs by means of catheterism of the air tubes, was first proposed and carried out by our associate member, Dr. Horace Green.

2d. The operation may be performed by the dexterous surgeon, with ease and facility, and with perfect safety to the patient.

3d. The results of this method of treatment, whether it has been employed in bronchial affections or in the commencement of tuberculosis, have already afforded the most gratifying indications that practical medicine will be greatly advanced by this discovery.

In the discussion on the reports of the committee, Dr. McNalty made the statement that as the result of many dissections he was able to prove that it was an anatomical impossibility to enter the larynx. This he proceeded to demonstrate by various diagrams and preserved specimens.

To this Dr. Sayre replied saying that "he was amazed that any man should come before the academy with a drawing and attempt to prove that it was an anatomical impossibility to enter the larynx, when every surgeon had been called upon to remove foreign bodies from the air passages; and if foreign bodies can get there by accident, why cannot the surgeon pass instruments intentionally?"

Dr. A. K. Gardner called attention to the well-known fact that, in the disease of chickens known as "pip," blunt-pointed wires armed with a pledget of cotton dipped in turpentine are passed into the trachea. The natural inference from his remarks would be that, if it is possible to pass the glottis in the lower animals, it is also possible in man.

Well did Dr. John Shanks say "The subject of discussion this evening is one, which, if precipitately acted upon by this academy, may, perhaps, cause many hereafter to regret, that they had not more deliberately, more perseveringly, and upon a larger and more extensive basis of tests and experiments, founded their opinions." After referring to the "hue and cry" that was raised against Horace Green when he first announced that he was able to enter the larynx and that since then his statement had been frequently confirmed, Dr. Shanks goes on to say, that he is "not at all surprised that the English and French allies, Professors Erichsen and Trousseau, are still before the walls of Troy." In other words they had not as yet acquired the necessary skill to pass the probang. Continuing, Dr. Shanks says: "I remember, many years ago, listening to a lecture delivered to his class, by the distinguished and learned chairman of the committee of this report. He was speaking of the introduction of the male catheter into the bladder, and in the course of his remarks took occasion to eulogize the practice of a Parisian surgeon, for the skill, rapidity, and address with which he performed this simple operation; and to say that it alone was worth a trip to Paris, to witness his execution of it. I must conclude, then, that that estimable gentleman, the chairman of the committee, has faith in the possibility of acquiring an eminent degree of skill and address in the use of catheters. Why, then, I would respectfully enquire, was there no allusion made to the possibility of the possession of this accomplishment by many of his contemporaries at home, in the catheterization of the air passages—a far more nice and intricate operation; and presenting a field equally as interesting, and less explored, for the exercise of American genius and talent; which—I may say without any sacrifice of modesty, as I am not a native born American—is second to none on the civilized globe?"

There was a good deal of haggling over the curve the probang should have in order to enter the larynx easily; for it was acknowledged that in some instances it did enter the larynx. The original curve as described by Horace Green was "one which will form the arc of one-fourth of a circle, whose diameter is four inches." The committee decided on a six-inch curve. Green, himself, stated that, although the four-inch curve made the introduction of the probang into the larynx more certain, it did not permit the passage of the probang beyond the vocal chords. He therefore lessened the curve and finally found that "by having the head of the patient thrown well back, so as to bring the mouth as near as possible on a line with the opening of the glottis, an instrument with the small curve, or nearly straight, may be introduced any required distance into the trachea with much ease, and ordinarily, with

much certainty." This position of the patient and form of probang permitted also the entrance of the probang into either bronchus.

When we compare this statement of position with that used by Brünings, for example, we see how far Horace Green had advanced in his technique. Moreover, entrance into the subdivisions of the bronchial tree can be actually demonstrated with the modern laryngoscope, and Brünings describes a case in which he passed a lead-tipped probe 2.5 mm. in diameter, a distance of 38.5 cm. and then made a röntgenogram of the probe *in situ*.

It was brought against Green that he stated that he could inject the bronchi and tubercular cavities in the lung. The experiments with the flexible tube, suggested to Green by Marshall Hall, led him to go a step further and, after introducing the tube, inject through the tube the solution of silver nitrate into the lung. The success attending this procedure suggested to the active mind of Green a possible treatment of tubercular cavities. I am unable to find in any of his published works, so far as they are available to me, a statement that he had made the attempt. He himself says that he had never made any such claim. . . . . He had on no occasion said that cavities could be, or had been injected; he had only suggested the enquiry "what should hinder this operation under favorable circumstances." Much that Green claimed could be done has been done, and who can say that some time in the future some such procedure may not be possible?

It is to be remembered that at this time the laryngoscope and röntgenograms were unknown, and Green could not demonstrate ocularly the things he claimed to do. Occasionally, however, a case presented itself in which the presence of the probang in the trachea could be demonstrated ocularly. A colleague of Green's, Dr. Carnochan, had under treatment a young man who had attempted suicide by cutting his throat. The wound never perfectly healed and a small, permanent opening into the trachea remained. Green at the request of Dr. Carnochan passed a sponge-tipped probang into the larynx, through the rima glottidis until it appeared at the opening in the trachea. He did the same thing on a patient who had been operated on for tracheotomy. In still another case, where there was a stricture of the œsophagus at the depth of four inches, he passed a probang down to the stricture and then passed a second probang for the distance of 10 inches into the trachea; still many remained convinced that the passage of a sponge-tipped probang into the larynx and trachea was an anatomical impossibility.

Reference has been made to the fact that a considerable number of the cases in which the committee attempted to pass the probang proved unsuccessful; the reason for the failure is not difficult to find. Dr. Green insisted on educating the throat, but the committee neglected this and "whenever the operation was performed by any of the committee, or by Dr. Taylor (one of the physicians at Bellevue Hospital where the experiments were made), it was done, ordinarily, by thrusting one or more fingers of the left hand into the mouth of the patient, and 'feeling for the epiglottis with the index finger'; retaining the finger in this position, the tube, stiffened by the wire, was passed over its extremity and the opening of the glottis felt for, with the curved end of the instrument. Of course 'direct irritation' was thus communicated to the nerves of the larynx, and a spasm of the glottis produced, with great certainty." The wonder is, not that the committee could not pass the tube, but that they ever succeeded in passing the tube.

Green defended himself vigorously before the academy, but much that he said is contained in the above abstracts. Dr. Willard Parker, chairman of the committee, said, "when he heard the paper read, he looked upon it as reflecting credit upon the author and upon New York surgery. He thought it true, until he investigated it. He would say, however, he thought the author honest, and that he thinks he does what he says he does. But he is deceived. There is no mistake about it." Like many other Americans, now as then, Dr. Parker was unable to judge, as Dr. Shanks had intimated, the merit of an American author and he would wait for an European verdict; "It will soon be settled by their voice."

But the midnight hour was passed and it was "the heated term." The committee rose and reported that they had discussed the subject given to their consideration, and referred it back to the academy. An attempt was made to take a vote of the academy on the subject, but it failed. Finally, on motion of Dr. Beadle, it was laid on the table; and there it still rests.

This seems to have ended, for the time being, the active campaign against Horace Green. It had been a bitter contest and one difficult to understand; in its course he had been compelled to resign from one of the medical societies of New York and just escaped expulsion from the Academy of Medicine (Wright). Green laid himself open to criticism by his faulty pathology; and yet, except in the origin of pulmonary phthisis from follicular pharyngitis, Morell Mackenzie supported him. In spite of the opposition and jealousy of many of the physicians in New York, Green built up a very lucrative practice, and, confining his work to laryngeal affections, became the first specialist in this country to devote himself to diseases of the throat.

I now pass to the vindication of Horace Green and the universal acceptance of the claim, which he was the first to put forward, namely, direct medication can be applied to the mucosa of the larynx, and either bronchus can be entered at will.

Bozzini, in 1807, devised a cumbersome instrument with which he claimed to be able to examine the various canals of the body. He, like Horace Green, was severely criticized, though the instrument seems to have done fair work. Babington, an Englishman, in 1829, used what he called a "Glottoscope" constructed on the same principle as the modern laryngeal mirror. Passing hastily over the succeeding 25 years I mention only by name, Liston, Baumes, Selligue, Ephraim Cutter and Avery, all of whom should be considered in an extended account of the development of the laryngoscope, and come to the year 1855, when Manuel Garcia pub-

lished his "Observations on the Human Voice" in which he describes the laryngeal mirror and its use. He used the sun's rays as the source of illumination. Garcia was called the "Father of Laryngoscopy" and lived to see his paper stimulate others to take up the work and develop the modern instruments which have enabled men, like Brünings, Jackson and others, to accomplish such wonderful results. On the occasion of Garcia's one hundredth birthday, laryngologists from all over the world gathered at London to do him honor. He died in 1906, in his one hundred and second year.

Two other names are to be considered in this connection, Ludwig Türck and Johan Czermak. The professional jealousy between these two was extreme. It must be granted that Türck used the instrument to the best advantage, but Czermak invented the concave head mirror with a perforation in its center. This did more to develop laryngoscopy than any other device and, as Czermak asserted, without it laryngoscopy would have been "a dead-born child."

In 1859, Störk described the technique of making laryngeal applications of nitrate of silver with the aid of the laryngoscope, and the contention of Horace Green was conclusively settled without further argument.

In 1863, Louis Elsberg presented before the New York Academy of Medicine the results of his laryngoscopic studies and observations. It was before this body of medical men that Horace Green so persistently and courageously defended his claim that the larynx could be entered. He lacked the ocular demonstration, but the laryngoscope now proved the correctness of his contention. The medical profession of these United States should feel honored that it can claim such men as McDowell, Green, Sims and others who have been pioneers in scientific medicine.

As stated in the early part of this paper, Horace Green died in November of 1866. At the meeting of the New York Academy of Medicine held January 2, 1867, the president, James Anderson, one of the members of the committee appointed by the academy to investigate Horace Green's paper who did not sign either the majority or the minority report, announced the death of Horace Green. After this Dr. E. R. Peaslee gave a brief sketch of Dr. Green, from which I take the following abstracts:

Horace Green was no ordinary man. His death covers a large circle of social and professional friends with gloom and by it this Academy is deprived of one of its most distinguished members. At home and abroad his valuable labors in his special department have been recognized and appreciated, and henceforth his name will be enshrined in American Medical History, and be reverenced as a large contributor to the advancement of the profession to which his energies were devoted.

As a physician, he was a bold and self-reliant practitioner. His self-reliance was doubtless due to his early education; but he was also compelled to rely mainly on himself, from the fact that he was, I may say, the pioneer in the application of local remedies to the respiratory passages. His work on bronchitis, published 20 years ago was the first systematic work on that subject. The small and fragmentary work of Trousseau and Belloc had preceded it, I think, by about five years. The opposition with which he at first met, required no small degree of boldness and self-reliance to overcome and outlive it.

No motives of mere policy ever actuated Dr. Green in his professional relations. He acted always on a thorough conviction of the truth of what he professed, respecting his peculiar method of treatment. Had he been a politic man he would not have gone to Bellevue Hospital, as he did, to attempt to pass the sponge-probang into the tracheæ of patients who had never before been operated on, without previously doing himself the justice to explain that it is generally necessary to accustom the laryngeal mucous membrane to the contact of the instrument before it would pass through the rima glottidis. For he was fully aware that most of those present did not admit that this operation is ever possible, except by mere accident. But he only thought of the practical importance of the operation he professed frequently to have accomplished, and trusted to his experience against the odds arrayed against him. That experience, however, did not, even under these circumstances, fail him.

As a man, Dr. Green was also kind hearted, generous, and transparently honest; though, by such as could not understand him, he was represented to be a crafty, deceptive, and calculating man. As a citizen, Dr. Green was liberal, high toned, and loyal; and in his family, both as a husband and a father, he was affectionate, indulgent, and considerate, and was beloved as but few men are.

Finally, and best and greatest of all, Dr. Green lived and died a sincere, consistent, and humble Christian. And who of us shall leave a higher or a purer record than he, when we in our turn shall follow him.

The following resolutions were then proposed by Dr. Peaslee and adopted by the academy:

Resolved, That the New York Academy of Medicine proudly claims the late Dr. Horace Green as one of its most distinguished fellows, recognizing him as one of its most useful members, as an accomplished physician, a bold and independent writer, a successful teacher, a courteous gentleman, and an honest man.

Resolved, That with unfeigned grief we regret his loss, as one of our associates, as a member of our noble profession, and as a fellow man; and we hereby tender to the bereaved friends our sincere sympathy and condolence.

Resolved, That these proceedings be entered on the minutes of the Academy, and that a copy be transmitted to the family of the deceased.

In his later years there were times when Horace Green had to defend himself against charges other than those we have been considering, which were wrongfully brought against him; but he successfully overcame them and he stands before us a true pioneer in American medicine.

NOTES

Castleton Medical College was established in 1818, and was known as Castleton Medical Academy until 1821, when its name was changed to the Vermont Academy of Medicine. In 1841, its name was again changed and, until it went out of existence in 1861, it was called Castleton Medical College. It had 350 graduates.

The full title of the book Green published in 1846 is, "A Treatise on Diseases of the Air Passages: comprising an Inquiry into the History, Pathology, Causes, and Treatment of those Affections of the Throat called Bronchitis, Chronic Laryngitis, Clergyman's Sore Throat, etc., etc. By Horace Green. New York and London, 1846." This title is, naturally, too lengthy to be placed on the back of a book of 272 pages; the publisher, therefore, condensed it to "Green on Bronchitis, etc." This may, possibly, have occasioned the severe criticism in the Boston

Medical and Surgical Journal where it is called a "misnomer." If so, then the reviewer was far from impartial in his judgment of the book.

RATIONAL SIGNS OF THE MAJORITY REPORT

PROBANG IN TRACHEA	PROBANG IN ŒSOPHAGUS
(1) Suffusion of the face rapidly increasing to turgescence and lividity.	(1) Suffusion of face slight; subsiding, with cessation of retching and cough.
(2) Great anxiety and alarm, not easily pacified.	(2) Little anxiety, easily pacified.
(3) Eyes wild, staring and overflowing with tears.	(3) Eyes natural, slight suffusion from tears.
(4) Cough violent and spasmodic.	(4) Little or no cough.
(5) Respiration greatly disturbed; inspiration loud, hoarse, and stridulous; expiration attended with violent cough, like that of laryngeal phthisis; ejection of bronchial mucus through the tube, and finally, free breathing through the tube.	(5) Respiration little, if at all, disturbed; occasional puffs of air through the tube.
(6) Voice extinguished; a hoarse whisper, interpreted with difficulty.	(6) Voice distinct, often quite natural.
(7) Retching slight.	(7) Retching and vomiting a common symptom.

FIGURES FROM THE MAJORITY AND MINORITY REPORT

MAJORITY

Trials	Failed	Succeeded	% of failures
71	58	11	81
	Hutchings' tube; large curve		
18	3	8	38
	Hutchings' tube; small curve		
38	35	3	92
	Sponge probang		
18	18		100

MINORITY

Dr. Barker accepts, for this occasion only, the figures of the majority. He quotes from the secretary's report giving the number of each individual case.

Failed	Doubtful	Successful
9	4	9

These 22 patients were experimented on with the tube. Dr. Barker comments on the surroundings and physical and mental condition of the patients.

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1854. Green, Horace: On the employment of injections into the bronchial tubes, and into tubercular cavities of the lungs. American Medical Monthly, Vol. III.

1855. Reports of the special committee to which the paper of Dr. Horace Green, on "Injections into the bronchial tubes, and into tubercular cavities of the lungs," was referred. Majority and minority report. Transactions of the New York Academy of Medicine, Vol. I.

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THE CORRELATION OF X-RAY FINDINGS AND PHYSICAL SIGNS IN THE CHEST IN UNCOMPLICATED EPIDEMIC INFLUENZA

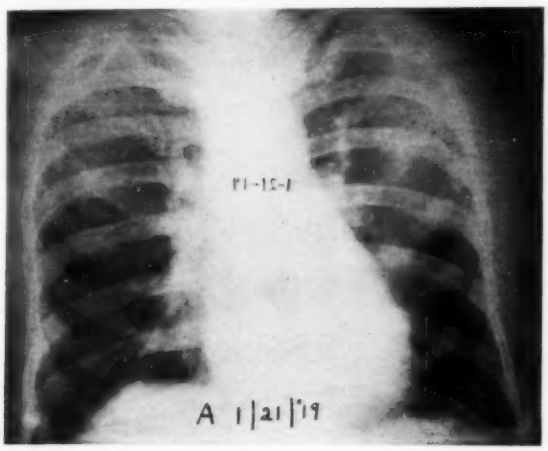
By ARTHUR L. BLOOMFIELD and CHARLES A. WATERS

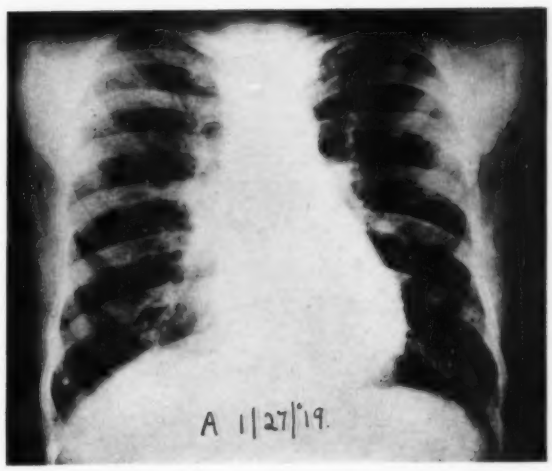
(From the Medical Clinic and the X-Ray Department of The Johns Hopkins Hospital)

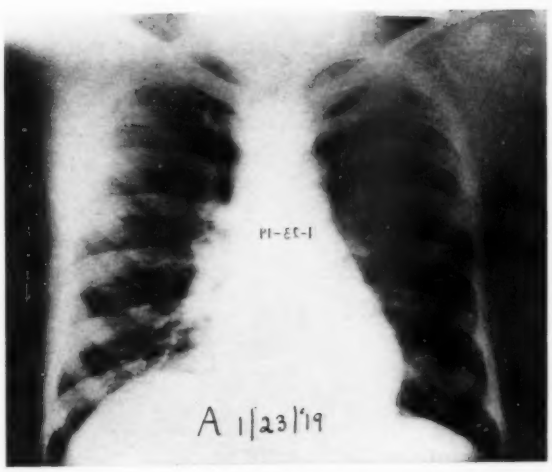
The exact significance of the pulmonary lesions associated with epidemic influenza is still a disputed question. In a recent report[1] the view was expressed that bronchopneumonia, although occurring frequently along with or following influenza, was not an essential feature of the disease, but a complication. This opinion was based on the study of an epidemic of severe cases most of which ran their course without demonstrable pulmonary involvement. It seemed possible, however, that small areas of pneumonia might exist even without cough, sputum, or physical signs, especially in the cases in which fever persisted for more than three or four days. The present study was undertaken to see what light roentgenographic examinations would throw on this question.

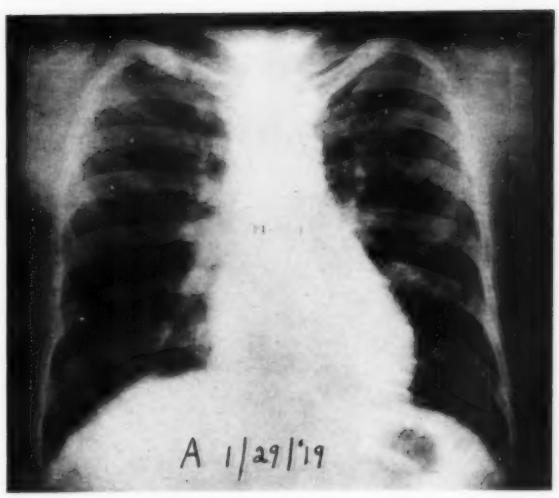
The material consisted of 16 consecutive cases of uncomplicated epidemic influenza treated in the wards of The Johns Hopkins Hospital during January and February, 1919. The diagnosis was based on the symptoms, the hyperæmic phenomena of skin and mucous membranes, the course of the disease, the duration of the fever, and the presence of leucopenia. In no case was there any evidence of pulmonary complications—the lungs remained clear throughout on physical examination, and cough, if present, was dry and productive only of the usual slight mucoid expectoration associated with the hyperæmia of the mucosa of the upper respiratory tract.

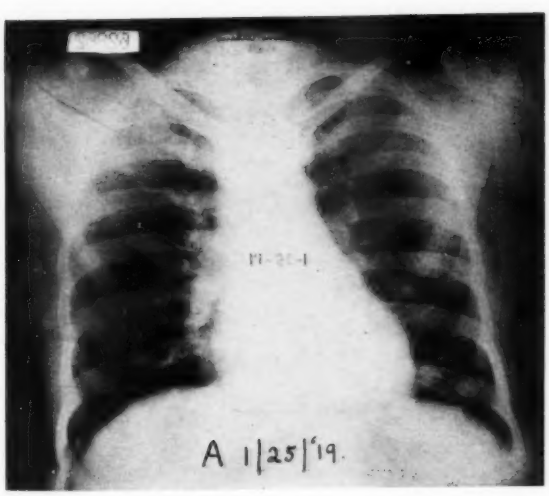
[1] Bloomfield A. L. and Harrop, G. A., Jr.: Bull. J. H. H., 1919, XXX, 1.

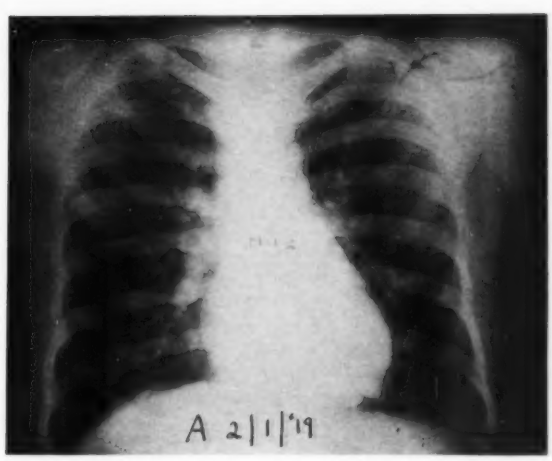












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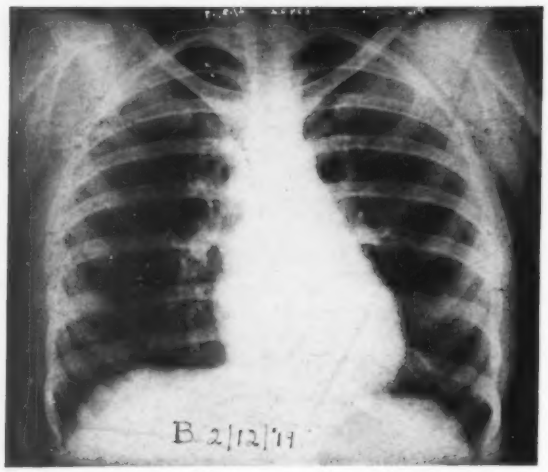

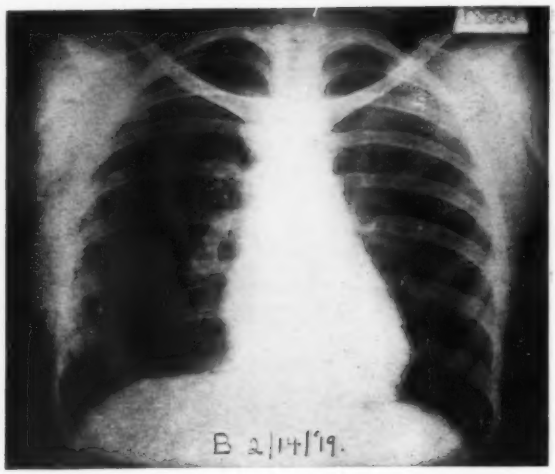

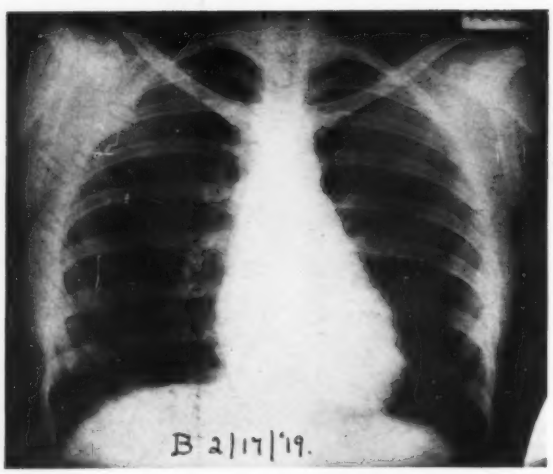

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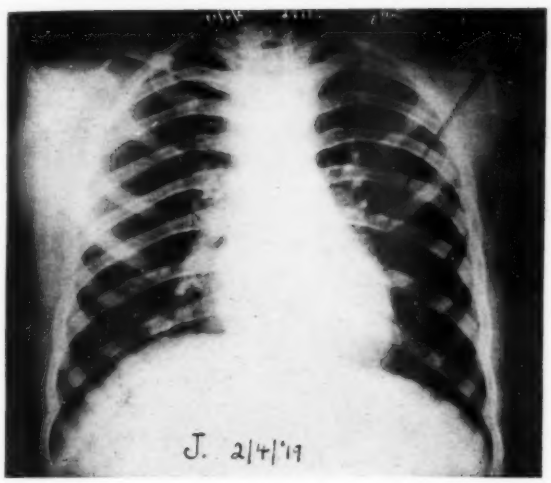

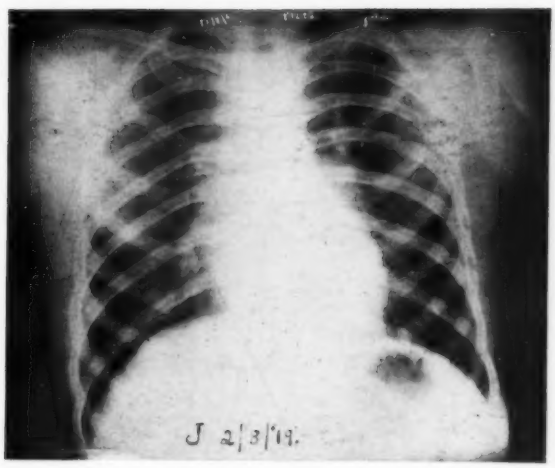

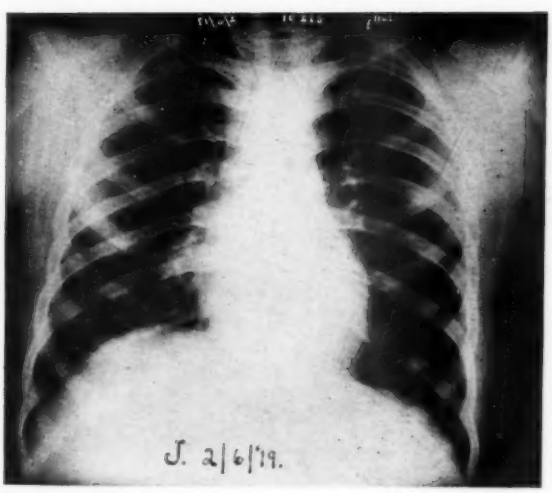

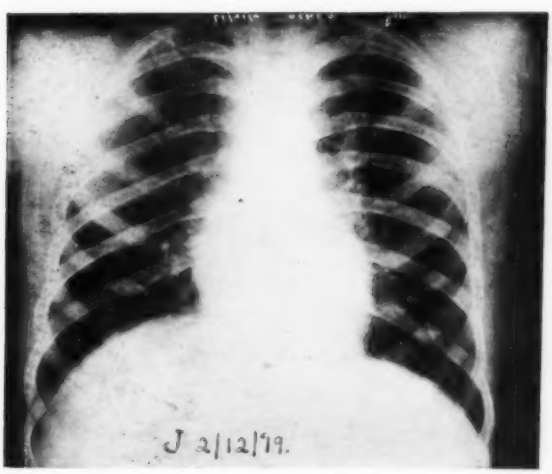

SERIES OF PLATES FROM CASE J.

TABLE I

COMPARISON OF CLINICAL AND ROENTGENOGRAPHIC EXAMINATION OF THE CHEST IN UNCOMPLICATED CASES OF EPIDEMIC INFLUENZA

Name	Date of examination	Day of disease	Temperature F°	Physical signs	Cough	Sputum	Day on which temperature became normal	Roentgenograms
V. A..	January 22	4	104°	Normal	Slight, dry	0	5	No signs of consolidation. Well marked root shadows on both sides. Apices clear. Bases clear.
	" 24	6	Normal	"	" "	0	.....	Pulmonary field shadows remain unchanged.
	" 27	9	"	"	0	0	.....	" " " " "
	" 30	11	"	"	0	0	.....	" " " " "
M. A..	January 22	4	102°	Normal	Slight, dry	Slight, mucoid	8	No signs of consolidation. Well marked root shadows on both sides. Apices clear. Bases clear. Calcified glands (?) at root of right lung.
	" 24	6	101°	"	" "	" "	.....	Pulmonary field shadows remain unchanged.
	" 27	9	Normal	"	0	0	.....	" " " " "
	" 29	11	"	"	0	0	.....	" " " " "
A.....	January 21	4	104°	Normal	Slight, dry	0	9	No signs of consolidation. Marked root shadows on both sides. Apices clear. Bases clear.
	" 23	6	103°	"	" "	0	.....	Pulmonary field shadows remain unchanged.
	" 25	8	102°	"	" "	0	.....	" " " " "
	" 27	10	Normal	"	" "	0	.....	" " " " "
	" 29	12	"	"	0	0	.....	" " " " "
	February 1	15	"	"	0	0	.....	" " " " "
W....	February 11	4	104°	Normal	Slight	Slight, mucoid	6	No signs of consolidation. Very marked root shadows on both sides. Apices clear. Bases clear.
	" 12	5	100°	"	"	" "	.....	Pulmonary field shadows remain unchanged.
	" 14	7	Normal	"	0	0	.....	" " " " "
	" 17	10	"	"	0	0	.....	" " " " "
	" 20	13	"	"	0	0	.....	" " " " "
N. B..	February 10	4	101°	Normal	Slight	Slight, mucoid	9	No signs of consolidation. Marked root shadows on both sides. Apices clear. Bases clear.
	" 12	6	100°	"	"	" "	.....	Pulmonary field shadows remain unchanged.
	" 14	9	100°	"	"	" "	.....	" " " " "
	" 17	12	Normal	"	"	" "	.....	" " " " "
	" 20	15	"	"	0	0	.....	" " " " "
S. C...	February 11	3	101°	Normal	Slight, dry	0	6	No signs of consolidation. Marked root shadows on both sides. Slight clouding of right apex. Bases clear.
	" 13	5	101°	"	" "	0	.....	Pulmonary field shadows remain unchanged.
	" 17	9	Normal	"	0	0	.....	" " " " "
	" 20	12	"	"	0	0	.....	" " " " "
D.....	February 5	8	102°	Normal	Slight, dry	0	9	No signs of consolidation. Very marked root shadows on both sides. Calcified glands (?) in left root. Apices clear. Bases clear.
	" 7	10	Normal	"	" "	0	.....	Pulmonary field shadows remain unchanged.
	" 10	13	"	"	" "	0	.....	" " " " "
	" 12	15	"	"	0	0	.....	" " " " "
J.....	February 4	4	101°	Normal	Slight	Moderate muco-purulent	8	No signs of consolidation. Marked root shadows on both sides. Apices clear. Bases clear.
	" 6	6	103°	"	"	"	.....	Pulmonary field shadows remain unchanged.
	" 8	8	Normal	"	"	"	.....	" " " " "
	" 12	12	"	"	0	0	.....	" " " " "
C.....	February 11	4	102°	Normal	Slight, dry	0	8	No signs of consolidation. Very marked root shadows on both sides. Apices clear. Bases clear.
	" 13	6	101°	"	" "	0	.....	Pulmonary field shadows remain unchanged.
	" 15	8	Normal	"	0	0	.....	" " " " "
	" 17	10	.....	"	0	0	.....	" " " " "
S.....	February 15	4	102°	Normal	0	0	5	No signs of consolidation. Very marked root shadows on both sides. Apices clear. Bases clear.
	" 18	7	Normal	"	0	0	.....	Pulmonary field shadows remain unchanged.
	" 24	13	"	"	0	0	.....	" " " " "
F. B..	February 12	6	100°	Normal	0	0	6	No signs of consolidation. Marked root shadows on both sides. Apices clear. Bases clear.
	" 14	8	Normal	"	0	0	.....	Pulmonary field shadows remain unchanged.
	" 17	11	"	"	0	0	.....	" " " " "
W. I..	February 10	3	100°	Normal	0	0	4	No signs of consolidation. Marked root shadows on both sides. Apices clear. Bases clear.
	" 12	5	Normal	"	0	0	.....	Pulmonary field shadows remain unchanged.
	" 14	7	"	"	0	0	.....	" " " " "
M. I..	February 8	4	101°	Normal	0	0	5	No signs of consolidation. Moderately marked root shadows on both sides. Apices clear. Bases clear.
	" 10	6	Normal	"	0	0	.....	Pulmonary field shadows remain unchanged.
	" 12	8	"	"	0	0	.....	" " " " "
G.....	January 25	4	102°	Normal	Slight	0	5	No signs of consolidation. Moderately marked root shadows on both sides. Apices clear. Bases clear.
	" 27	6	Normal	"	"	0	.....	Pulmonary field shadows remain unchanged.
	" 29	8	"	"	0	0	.....	" " " " "
P.....	February 1	4	100°	Normal	0	0	4	No signs of consolidation. Well marked root shadows on both sides. Apices clear. Bases clear.
	" 3	6	Normal	"	0	0	.....	Pulmonary field shadows remain unchanged.
	" 5	8	"	"	0	0	.....	" " " " "
W. A..	February 1	4	102°	Normal	0	0	6	No signs of consolidation. Well marked root shadows on both sides. Apices clear. Bases clear.
	" 3	6	Normal	"	0	0	.....	Pulmonary field shadows remain unchanged.
	" 5	8	"	"	0	0	.....	" " " " "

Roentgenographic examination of the chest was made as soon as possible after admission and thereafter at two- or three-day intervals until the patient was discharged. Each series of plates was studied with two points in mind—first to discover and interpret any abnormal markings, and secondly, to determine any variations in the pulmonary shadows during the course of the disease.

RESULTS

The results of the examinations are summarized in Table I. In no case was there any detectable change in the appearance of the lung markings in a series of from three to six plates made at various times during the febrile and post-febrile convalescent stages of the disease. It would seem, therefore, that the markings were permanent or at least unassociated with the immediate acute disease. In no case was any shadow seen which could be interpreted as indicating a solidification of the lung. The usual grades of root shadows, in some cases small areas of probable calcification (glands ?) resulting from infections prior to the influenza, and in others slight degrees of apical clouding were seen. It is not the present purpose to discuss the exact significance of pulmonary shadows in general.

CONCLUSIONS

1. Repeated roentgenographic examinations of the lungs during the course of clinically uncomplicated cases of epidemic influenza showed only permanent lung markings.

2. These findings support the clinical impression that bronchopneumonia is a complication and not an essential feature of the disease.

DR. GEORGE PEIRCE

By J. H. Mason Knox, Jr.

On February 4, 1919, Dr. George Peirce, associate chemist of the manufacturing firm of Colgate and Company, Jersey City, New Jersey, died as the result of extensive burns received following an explosion of ether vapor.

The details of the accident could not be accurately ascertained. It is known, however, to have been due to an electric spark discharged in a room in which the Griguard reaction, in which ether is employed, was being carried on.

Following the initial explosion, Dr. Peirce escaped from the building, but re-entered the burning laboratory thinking probably to put out the fire, which was endangering the lives of those in the building, or to save some apparatus. Shortly afterwards he was seen running out with his clothes all ablaze.

Help was near at hand, but before the fire could be extinguished he had suffered severe burns over a large portion of his body and died within a few hours after his removal to the hospital.

The life of Dr. Peirce was one of peculiar simplicity and charm. In the most unostentatious manner he became engrossed in studies in higher organic chemistry to which his inclination and ability seemed to direct him. Dr. Peirce was born in Bristol, Pennsylvania, May 7, 1883. He was the son of Harold Peirce and Charlotte Converse Peirce, now living at Haverford, Pa. From his parents he inherited a devotion to high ideals and a kindly tolerance which were conspicuous qualities in his character. He was the oldest of five children and grew up in the stimulating atmosphere of a home of culture and one given to hospitality.

He prepared for college at the Germantown Academy and graduated at Haverford College with the class of 1903. Here he was holder of the corporation scholarship and a member of the Phi Beta Kappa Society. He immediately entered The Johns Hopkins Medical School and received the degree of M. D. in 1907. In both college and medical school his course was marked by strict application to his duties. He had time, however, to form a number of warm friendships with men of studious habits who found in Peirce a man who took a real and unselfish interest in their plans.

My own boyhood associations with his father were repeated in the son, as he came regularly to my home to dine each Sunday. On these occasions and on the walks which frequently followed, his absorbing interest in his work, his singleness of purpose and his generous judgment of others were outstanding characteristics.

The originality of his thinking was early evinced. He published later a short paper read before the American Mathematical Society, while still an undergraduate at Haverford, and while in the medical school, in association with Dr. Loevenhart, he carried out a valuable research on lipase.

After his graduation in medicine he had charge of St. Anthony's Hospital, Newfoundland, organized by Dr. Grenfell.

Later he obtained an internship in the Pennsylvania Hospital, Philadelphia, where he remained for two years as resident physician.

In 1910 he married Miss Ethel Girdwood, of West Orange, New Jersey, who had also been a student of The Johns Hopkins Medical School. In his wife Dr. Peirce found a devoted and sympathetic helpmate who encouraged him in all his subsequent work. Together they went to Germany where Dr. Peirce continued his chemical studies at the University of Berlin, working under the direction of Emil Fischer and other well-known chemists, while Mrs. Peirce served as voluntary assistant at the Kinderklinik of the celebrated Dr. Hübner. After two years he received the degree of Ph. D. in the university, having presented a thesis on "The Alkaloids of the Brucin Group."

Returning to America he accepted an appointment in the University of Wisconsin as assistant in physiology. The following year he was made instructor in pharmacology. Besides his teaching duties Dr. Peirce carried out researches on the ferments and some of the higher monosaccharides.

In 1914 he returned to The Johns Hopkins Medical School as instructor in urology, in charge of the chemical laboratory of the James Buchanan Brady Urological Institute, just completed. He organized and equipped the laboratory and conducted studies on the excretion of sugar by the kidneys.

Two years later, in 1916, he was asked to join the chemical department of Colgate and Company. There he was largely occupied in organic chemical research work in the terpene field and in related work. His associates in the laboratory testify to his "wide thorough knowledge of chemical subjects and of his ability to obtain the practical results he started after."

It was during the prosecution of his investigations that the accident occurred which resulted in his death.

This brief and incomplete sketch can convey only an inadequate idea of Dr. Peirce as he was known to his intimate friends.

He was exceptionally happy in his home life. In Mrs. Peirce he had a companion who because of her training was able to appreciate and further his scholarly ambitions. Three boys with their mother survive him. In this congenial atmosphere Dr. Peirce led the quiet, reserved career of a student. He was loyal to his friends and keenly interested in the march of events about him, but he found his greatest satisfaction in the chemical studies to which he had devoted his life.

In this department of science he had already made important contributions and seemed just at the threshold of his greatest power when he met his untimely end.

He will long be respected and remembered by those who knew him.

Dr. Peirce's published works are as follows:

"A Curious Approximate Construction for π." Bull. Am. Math. Soc., 2d Ser., 1901, VII, 426-427.

"The Inhibiting Effect of Sodium Fluoride on the Action of Lipase." Jour. Biol. Chem., 1907, II, 397.

"The Deviation of Ferment Action from the Monomolecular Law with Especial Reference to the Esterases." Jour. Am. Chem. Soc., 1910, XXXII, 1517.

"Ueber den Abbau des Brucins zu einer neuen Base Curbin und einige andere Versuche in der Brucinreihe." Inaug. Diss., Berlin, November, 1912.

"The Compound Formed Between Esterase and Sodium Fluoride." Jour. Biol. Chem., 1913, XVI, 5.

"The Partial Purification of the Esterase in Pig's Liver." Jour. Biol. Chem., 1913, XVI, 1.

"The Excretion of Sugar by the Kidney." Proc. Soc. Exp. Biol. & Med., May, 1915, XII.

"The Configuration of Some of the Higher Monosaccharides." Jour. Biol. Chem., 1915, XXIII, 327.

ESTIMATE OF SOME OF DR. PEIRCE'S PAPERS.

By PROFESSOR E. EMMET REID, The Johns Hopkins University.

Dissertation: "Ueber den Abbau des Brucins zu einer neuen Base Curbin und einige andere Versuche in der Brucinreihe," Berlin, 1912. (On the degradation of brucin to a new base, curbin, and some other experiments in the brucin series). A skillful piece of experimental work on a difficult and important problem. Although the end of the problem was not reached, a number of steps were taken towards the final solution and, so far as he went, clear and definite results were obtained.

"The deviation of ferment action from the monomolecular law with especial reference to the esterases" (J. Am. Chem. Soc., 1910, XXXII, 1517). A careful study of the rate of hydrolysis by lipase prepared from pig's liver. The velocity is found not to agree with the mass law if the reaction is considered a monomolecular one, in the ordinary sense, but it is shown that by regarding it as a two-stage reaction and assuming that the enzyme and ester form an intermediate compound the results obtained can be harmonized with the mass law.

"The inhibiting effect of sodium fluoride on the action of lipase" (J. Biol. Chem., 1907, II, 397). A large number of quantitative observations are made on the velocity of hydrolysis of a number of esters by lipase in the presence of varying amounts of sodium fluoride which is found to retard the reaction enormously. The amount of such retardation is found to vary greatly with the ester studied. Other salts were tried for comparison. A large number of interesting facts are brought out, the explanation of which will be found in a subsequent paper.

"The compound formed between esterase and sodium flouride" (J. Biol. Chem., 1913, XVI, 5). This paper is in effect a continuation of the one preceding, explaining the inhibiting effect of sodium fluoride by assuming that the sodium fluoride combines with the enzyme to form a compound that is no longer active. A large number of quantitative experiments are given, the results of which will agree well with this assumption.

"The configuration of the higher monosaccharides" (J. Biol. Chem., 1915, XXIII, 327). The configuration of galaheptose, mannoheptose and mannoctose are obtained. The paper shows a good working knowledge of the reactions in the sugar group and a number of difficult preparations were made. The results obtained fill in gaps in our knowledge of the sugars.

APPRECIATION OF THE MAN AND HIS WORK.

By PROF. JOHN J. ABEL, The Johns Hopkins Medical School.

In 1905 George Peirce spent part of a year in my laboratory engaged in a research under the direction of Dr. A. S. Loevenhart (The Inhibiting Effect of Sodium Fluoride on the Action of Lipase, Jour. Biol. Chem., XI, 5). It was then that I learned to know him and through numerous conversations with him I soon became convinced that he was a young man of great ability and of high promise for the future. His method of attacking a problem was that of an open-minded investigator and he early showed the capacity to seize upon the salient points of a problem and to separate them from their entangling alliances with troublesome non-essentials. His clear-sighted vision is well illustrated by the manner in which he rounded out his knowledge. After graduating from The Johns Hopkins Medical School, and serving as an interne and house officer in the Pennsylvania Hospital in Philadelphia, he saw that

he could not accomplish his purpose as an investigator unless he acquired a better theoretical and working knowledge of organic chemistry.

It is a pleasure to recall that I had the honor to be consulted by him at this critical step of his career. As the result of mature deliberation on his part and with the hearty sympathy of a wise father, Peirce decided to enter upon a thorough course in chemistry under the direction of Emil Fischer, Professor Leuchs and other leaders of chemical thought in the University of Berlin. This part of his career has already been referred to by Dr. Knox, and I speak of it here because I know that his years abroad were of the greatest intellectual value. He was, of course, well prepared to take up advanced work. His dissertation on brucin and his paper on the configuration of the higher monosaccharides give proof that he rapidly mastered the methods of organic chemistry.

His paper in collaboration with Norman M. Keith, on the excretion of sugars by the kidney, published in the Proceedings of the Society for Experimental Biology and Medicine, VIII, No. 8, appears to me to be his best piece of work. Here an entirely new hypothesis is offered in explanation of the excretion of sugars by the kidney. Many hypotheses have been advanced to account for the fact that normally only the minutest trace of sugar is present in the urine, whereas, if the blood sugar rises beyond a certain level, some will appear. However, none of these hypotheses have been generally accepted. Peirce believed that the true explanation is this: Sugar normally gains entrance into the kidney cells in proportion to its concentration in the blood. During its passage through the cell, some of it is oxidized and if not too much has entered the cell all of it will be oxidized and none appear in the urine. In testing out his hypothesis he made use of published figures for the concentration of various substances in the blood and urine and made some experiments of his own. He says, "We have found that very roughly speaking a dog of 10 k. body weight with a blood sugar content of 0.1 per cent should excrete about 0.7 gm. sugar per hour if the kidney were completely permeable and secreting freely. During marked diuresis Barcroft and Brodie found that about 660 c. c. of oxygen would be required by the dog's kidneys for the same period. 0.7 gm. of sugar requires 520 c. c. of oxygen for complete oxidation to CO_2 and water. The correspondence is fairly close."

He also estimated that the sugar content of the renal vein should be about 80-90 per cent of the sugar content of the renal artery if the kidney is completely permeable. As a matter of fact Peirce and Keith found by analyzing simultaneous samples of the blood from the femoral artery and renal vein, in five experiments, a difference of 10 to 15 per cent, in three experiments, no difference, and in two, a slightly higher content in the renal vein than in the artery. His studies led him to conclude that only the sugars that are oxidized by the body will show the so-called threshold phenomenon, and he feels justified in making the general statement: If the kidney is permeable for a sugar, when and only when its concentration in the blood rises beyond a certain level, that sugar is oxidized by the kidney. In a foot-note, he even ventures to suggest on purely theoretical grounds the following: If the kidney is permeable for any substance, when and only when its concentration in the blood rises beyond a certain level, that substance is metabolized by the kidney.

Had this young man of high promise been spared he would no doubt have carried out extensive researches in support of this novel hypothesis, and in time, when properly supported by experimental data, we may hope that it might have become known as Peirce's law.

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The Johns Hopkins Hospital Bulletins are issued monthly. They are printed by the LORD BALTIMORE PRESS, Baltimore. Subscriptions, $3.00 a year (foreign postage, 50 cents), may be addressed to the publishers, THE JOHNS HOPKINS PRESS, BALTIMORE; single copies will be sent by mail for fifty cents each. Single copies may also be procured from the BALTIMORE NEWS CO., Baltimore.